CSPI CENTER FOR SCIENCE IN THE PUBLIC INTEREST
Publisher of *Nutrition Action Healthletter*

January 30, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Advanced Notice Of Proposed Rulemaking: Substances Prohibited From Use In Animal Food Or Feed; Animal Proteins Prohibited In Ruminant Feed, 67 Fed. Reg. 67,572 (Nov. 6, 2002); Docket No. 02N-0273

Dear Dockets Management Branch:

The Center for Science in the Public Interest (CSPI) appreciates the opportunity to comment on possible changes by the Food and Drug Administration (FDA) to the current regulation prohibiting the use of certain proteins in ruminant animal feed. That rule is designed to prevent the spread through animal feed of the causative agent of bovine spongiform encephalopathy (BSE) if it were to enter or be present in the United States. CSPI is a non-profit consumer advocacy and education organization that focuses primarily on food safety and nutrition issues and is supported principally by approximately 800,000 subscribers to its *Nutrition Action Healthletter*.

In April 2001, the FDA announced its Action Plan for Transmissible Spongiform Encephalopathies (TSEs), a group of progressive neurological diseases that includes BSE (in cattle), scrapie (in sheep and goats), and Chronic Wasting Disease (CWD) (in deer and elk).[1]

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[1] FDA, Action Plan, *Transmissible Spongiform Encephalopathies including Bovine Spongiform Encephalopathy and Chronic Wasting Disease* (Apr. 24, 2001),[hereinafter FDA, *Action Plan*], available at <*http://www.fda.gov/oc/oca/roundtable/bse/FDA_actionplan.html*>.

The plan is intended to protect U.S. public health by, among other things, preventing the exposure of Americans to agents of TSEs through human and animal food products.[2] The consumption of BSE-infected cattle has been linked to variant Creutzfeldt-Jakob Disease (vCJD) disease in humans.

In its plan, the FDA has recognized that the function, biology, and pathology of prions – the proteins believed to be the causative agents of TSEs -- "are still largely unknown," and acknowledged that "what factors might cause or transmit TSEs are poorly understood."[3] It is precisely because scientific understanding concerning TSEs, including BSE, is inadequate that greater precautionary measures are needed to assure that the public's health is protected. Therefore, we urge FDA to take actions to strengthen and further reduce the risk that BSE could become established and amplified in the United States.

Below, we provide specific comments on aspects of the advanced notice of proposed rulemaking.

1. Specified Risk Material Should Be Excluded From Rendered Animal Products

The Harvard Risk Analysis has recognized that implementation of a ban on specified risk materials (SRMs) from the human and animal food chains has a "dramatic effect" on potential human exposure and the spread of BSE to cattle, reducing the predicted number of BSE cases in cattle by 80% and the potential human exposure by 95%.[4] To this end, the USDA's Food Safety and Inspection Service (FSIS) has published a document stating that it is considering classifying

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[2] FDA, *Action plan*, at p. 2.

[3] FDA, *Action plan,* at p. 4.

[4] Harvard Center for Risk Analysis, Harvard School of Public Health and Center for Computational Epidemiology, College of Veterinary Medicine, Tuskegee University, *Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States* (Nov. 26, 2001), at pp. iv & 96.

certain bovine tissues, such as brain and spinal cord from cattle aged 24 months and older and downer cattle regardless of age, as SRMs and prohibiting their use in human food because of their high infectivity.[5]

To further reduce any potential BSE risk, the FDA has asked whether it should consider banning SRMs from ruminants two years and older from use in rendered products. We believe that, at a minimum, the FDA should classify as SRM the central nervous system tissue and other potentially high-risk tissues of all cattle 12 months or older and prohibit their use in the rendering process. In addition, although the FDA has recently prohibited the use of animals diagnosed with CWD or at high risk for CWD in the rendering process, SRMs from all ruminant wildlife, regardless of age, should be eliminated from the rendering process. Finally, FDA should ban from the rendering process SRMs from all dead stock and downer cattle. These additional safeguards are needed for the following reasons:

- Central nervous system tissue, including the brain and spinal cord, contains the highest concentrations of the transmissible agent if an animal is infected with BSE or another TSE and have the highest degree of infectivity.[6] Therefore, keeping the most infective material out of the feed and food chain helps assure that the BSE or TSE agent is not recycled. This is particularly important with respect to dead stock and downer cattle since such animals in Europe have been

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[5] USDA, Food Safety and Inspection Service, *Current Thinking On Measures That Could Be Implemented to Minimize Human Exposure to Materials That Could Potentially Contain The Bovine Spongiform Encephalopathy Agent* (Jan. 15, 2002), at pp. 6 & 8-9 [hereinafter FSIS, *Current Thinking on BSE*].

[6] According to the Food and Agriculture Organization of the United Nations, specified risk materials, including bovine spinal cord, brain, eyes, tonsils and parts of the intestines account for over 95% of TSE infectivity. *See* FAO, *Mad cow disease: FAO recommends precautions* (8 February 2001), at p. 2, available at *<http://www.fao.org/news/2001/010202-e.htm>*.

shown to have a greater incidence of BSE.[7]

- The risk of a BSE-positive is higher in cattle over 24 months of age.[8]

According to the European Commission's Scientific Steering Committee, the age of an animal represents "a good approximation of the potentially possible incubation stage and hence its infective load."[9] However, it is not known at what stage of incubation a TSE can be detected in a post-mortem test.[10] TSEs have long incubation periods and even an animal that tests negative could be harboring infectious prions. Therefore, as long as it cannot be demonstrated that an animal is not incubating BSE, SRMs from cattle over 12 months of age should not become part of the animal or human food chain through the rendering process.

- USDA's Animal and Plant Health Inspection Service (APHIS) has reported confirmed cases of scrapie in sheep and goats in the United States for decades.[11] More recently, chronic wasting disease, a naturally occurring disease in elk and deer, has been found in animals in Colorado, Wyoming, Minnesota, New Mexico, Nebraska, Wisconsin, Montana, South Dakota, Kansas, Illinois, and Oklahoma. It also appears that the incidence of CWD in wild deer and elk

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[7] 68 Fed. Reg. 2703, 2704 (Jan. 21, 2003) (USDA, APHIS, Advanced Notice of Proposed Rulemaking: *Risk Reduction Strategies for Potential BSE Pathways Involving Downer Cattle and Dead Stock of Cattle and Other Species*).

[8] In Europe, approximately 99.95% of the over 180,000 BSE cases have occurred in animals over 30 months of age. *See* European Commission, Health and Consumer Protection Directorate-General, Press Release, *Commission approves further protection measures against BSE* (Brussels, 7 February 2001), available at <*http://www.europea.eu.int/comm/dgs/health_consumer/library/press/press106_en.html*>.

[9] European Commission, *Final Opinion of the SSC on the Geographical Risk of Bovine Spongiform Encephalopathy (GBR), adopted on July 6, 2000, at p. 33.*

[10] According to FSIS, given the limitations of the diagnostic tests currently available, "certain tissues of cattle infected with BSE may contain the BSE agent before a diagnostic test could indicate that the animal has BSE." *See* FSIS, *Current Thinking on BSE*, at p. 10.

[11] USDA, Animal and Plant Health Inspection Service, *Scrapie,* (Feb. 2002), <*http://www.aphis.usda.gov/ipa/pubs/fsheet_faq_notice/fs_ahscrapie.html.*>

has been rising, with cases east of the Mississippi River found for the first time last year.[12]

Even though the FDA has prohibited using CWD-positive or high-risk elk and deer in animal feed or feed ingredients, we believe these protections do not go far enough. SRMs from ruminant wildlife of any age as well as from downer and dead animal stock should not be permitted in the rendering process because it is currently impossible to know whether such animals may be incubating a TSE.

- While most TSEs are species specific, with no evidence that they can be or have been transmitted to humans, the Centers for Disease Control and Prevention have stated with respect to CWD that there is not yet strong evidence that such transmission could not occur. For BSE, however, there is epidemiologic and laboratory evidence indicating that it has been transmitted to humans, causing vCJD. Accordingly, in the absence of more complete scientific evidence concerning which TSEs can cross which species barriers, the safest course is to prohibit SRMs from cattle over twelve months of age, ruminant wildlife of any age, and dead stock and downer cattle from the rendering process. This is the only way to ensure that TSE-infectivity does not inadvertently enter the animal or human food chain.

- Although the USDA has increased testing for BSE, only a small portion of cattle that are nonambulatory, show signs of neurological disease, or die on the farm are tested for BSE. Even then, the rapid post-mortem tests currently in use only identify the presence of the BSE agent near the end of the incubation period and do not identify pre-clinical cases at earlier stages of incubation. These tests are approved for use on animals over 30-months old and are not

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[12] USDA, Animal and Plant Health Inspection Service, *Chronic Wasting Disease* (Nov. 2002), at *http://www.aphis.usda.gov/oa/pubs/fscwd/html>;* Wisconsin Department of Natural Resources, *Chronic Wasting Disease and Wisconsin Deer* (Rev. Jan. 14, 2003), at *<http://www.dnr.state.wi.us/org/land/wildlife/whealth/issues/CWD>.*

deemed reliable for animals under that age.[13] As a result, the current testing program may be inadequate to detect latent BSE in U.S. cattle or TSEs in other ruminants. Banning SRMs from cattle over 12 months of age, all ruminant wildlife, such as deer and elk, and all dead or downer cattle would provide an additional safeguard against inadvertent introduction of TSE agents into the human and animal food chain.

- Prions are highly resistant to methods that kill or inactivate other disease-causing agents. According to USDA's Animal and Plant Health Inspection Service (APHIS), if a TSE-agent is present in a rendered product, the continuous rendering process most used in the United States will only reduce TSE infectivity by two logs or less, while batch rendering will reduce infectivity by three logs.[14] Accordingly, some TSE agent can survive the rendering process.

Therefore, until there is a proven technology to destroy the TSE agent during rendering, the most protective approach is to prohibit SRMs from cattle 12 months and older, ruminant wildlife, and dead stock and downer cattle from the rendering process. Banning the use of SRMs from these animals would help assure that the TSE agent does not enter the animal or human food chain.[15]

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[13] Official Journal of the European Communities, Court of Auditors, *Special Report No. 14/2001, Followup to Special Report No. 19/98 on BSE, together with the Commission's replies* (2001/C 324/01, at p. 11, n.(1).

[14] 68 Fed. Reg. at 2703.

[15] The capacity of an individual rendering plant to eliminate the agent can vary depending on plant operating conditions and whether there are process breakdowns. One commentary has noted that data from studies on the rendering process conducted in the UK and the Netherlands have suggested that the hyperbaric 133° C rendering process is likely to be effective if high risk materials, such as brain and spinal cord, are excluded from the process. *See* Taylor, D.M., *Issues Involving the Disposal of TSE Infected Animals*, Presented at the United States Animal Health Association 2001 Annual Meeting, available at *http://www.usaha.org/speeches/speech01/s01tay12.html*>.

• The risk associated with mixing SRMs with other kinds of waste also warrants a ban on the use of SRMs from ruminants in the rendering process. Handling, storage and separation procedures may be inadequate or insufficient to prevent mixing. Thus, as long as rendering plants do not have separate facilities for the production of animal feeds, specified risk material should be excluded to prevent unintentional mixing. The greater the safety of the source material, the greater the safety of the final products.[16]

2. The Use Of Poultry Litter In Cattle Feed Should Be Prohibited

Poultry litter, in particular broiler litter, is used as a feed ingredient for cattle because of its nutritional value and its economical cost.[17] "Broiler litter consists of bedding (wood shavings, rice hulls, peanut hulls, etc.), manure, and feed spilled by the birds to the floor of the house."[18] Spilled feed can contain prohibited mammalian proteins in the form of meat and bone meal (MBM) since MBM may be fed to poultry, as well as pigs and horses.[19] Indeed, the poultry and swine industries are the predominant consumers of meat and bone meal.[20] Because the prohibited protein could pass through the birds' digestive tracts, the BSE-agent, if present, could be recycled to cattle through poultry waste or poultry carcasses that are in the litter. In addition, spilled feed in poultry litter could contain mammalian protein.

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[16] If FDA determines to prohibit SRMs in the rendering process, it also should require renderers to provide documentation and adequate recordkeeping concerning the proper disposal of materials designated as SRMs.

[17] D.S. Doctorian and G.W. Evers, *Using Broiler Litter as a Protein and Mineral Supplement for Beef Cows*, Texas A & M University Agricultural Research & Extension Service (Rev. Jul. 15, 1997), available at *<http://overton.tamu.edu/forage-livestock.1996/litutil.html>*.

[18] S.C. Smith and J.D. Enis, *Poultry Litter: Forage and Livestock Considerations*, Oklahoma State University Extension Facts F-8111, p. 1.

[19] 21 CFR § 589.2000.

[20] R.D. Miles and J.P. Jacob, *Using Meat and Bone Meal in Poultry Diets*, University of Florida Cooperative Extension Service Factsheet PS-28 (Aug. 1998), p. 2.

Although there is no reliable evidence that poultry are susceptible to developing symptoms of prion diseases,[21] recent studies indicate "that the absence of clinical symptoms does not necessarily exclude transmission of prion disease across a species barrier" and suggest that subclinical or long preclinical carrier states exist in apparently resistant species.[22] For example, one study has found that hamster prions thought to be nonpathogenic for conventional mice could cause "prion replication to high levels in such mice but without causing clinical disease" in the mice.[23] The prions from these mice where shown to cause a TSE in hamsters.[24] Thus, "BSE passaged in species other than cattle also may be pathogenic to humans" or to cattle.[25]

In addition, there is evidence that the host range of a prion disease can be altered on passage through certain species. Mule deer CWD is ordinarily not transmissible to Syrian golden hamsters. However, when ferrets were inoculated with CWD and then Syrian golden hamsters were inoculated with the ferret-passaged CWD, the Syrian golden hamsters developed a prion disease.[26] Accordingly, the possibility of transmission of the infectious agent that causes BSE or another TSE from asymptomatic poultry to an unknown range of species cannot be ruled out.

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[21] R.J. Cawthorne, *Failure to confirm a TSE in chickens*, 141Veterinary Record 203 (Aug. 1997); European Commission, Scientific Steering Committee, *Report on the Risk Born by Recycling Animal By-Products as Feed with Regard to Propagating TSE's in Non-ruminant Farmed Animals* (Adopted September 1999).

[22] A. Hill and J. Collins, *Species-Barrier-Independent Prion Replication in Apparently Resistant Species*, 110 APMIS, 44-53 (Jan. 2002).

[23] Andrew Hill et al. *Species-Barrier-Independent Prion Replication in Apparently Resistant Species*, 97 Proceedings of the National Academy of Sciences 10248-10253 (Aug. 2000) [hereinafter PNAS article].

[24] PNAS article.

[25] PNAS article.

[26] J.C. Bartz, et al., *The Host Range of Chronic Wasting Disease is Altered on Passage in Ferrets*, 251 Virology 297-301 (1998).

Although infectious prions have not been found in the feces of cattle or other animals,[27] there is evidence that prions can be present in urine. Researchers in Israel found a component of the prion in the urine of hamsters, cattle, and humans suffering from TSEs.[28] In addition, contaminated saliva, urine, or feces are often cited as possible mechanisms for the transmission of CWD among deer and elk.[29] According to the University of Minnesota, the "pattern of transmission and association of prions with lymph tissue in the mouth and intestinal tract has led to the hypothesis that the CWD agent may find its way through saliva, feces and urine onto grasses and other food. Deer eating contaminated food may contract the disease."[30] Therefore if poultry consume infectious prions, the possibility that their waste products (urine and feces) might contain these prions cannot be ruled out.[31]

Finally, while proper processing can destroy more common pathogens harbored by the litter, there is no evidence that this same processing would destroy the BSE agent if it were present in the litter. The most common method for killing pathogens in litter is a process called

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[27] European Commission, Scientific Steering Committee, *Listing of Specified Risk Materials: a Scheme for Assessing Relative Risks to Man* (Rev. Jan. 1998).

[28] Gideon M. Shaked, et al., *A Protease Resistant PrP Isoform is Present in Urine of Animals and Humans Affected with Prion Diseases*, Journal of Biological Chemistry (June 21, 2001).

[29] Michigan Department of Natural Resources, *Chronic Wasting Disease*, Brochure (Aug. 6, 2002); University of Minnesota Extension Service, *Chronic Wasting Disease: Frequently Asked Questions* (Nov. 5, 2002); Alberta Agriculture, Food and Rural Development, *Chronic Wasting Disease (CWD) of Elk and Deer* (Rev. Dec. 2002).

[30] Center for Animal Health and Food Safety, University of Minnesota, *Key Information About Chronic Wasting Disease (CWD)* (rev. March 5, 2002).

[31] The Scientific Steering Committee of the European Commission has concluded that the possibility of active replication of prions in birds is remote, but that necrophagous "birds are nevertheless able to ingest BSE infectious material and to spread the ingested infectious material through dissemination of faeces because it is unlikely that the pathological prion protein would be destroyed in the digestive tract." European Commission, Scientific Steering Committee, *Opinion on Necrophagous Birds as Possible Transmitters of TSE/BSE* (Adopted November 2002).

"deep stacking" which generally results in the heating of a stack of litter to between 140 and 160 degrees Fahrenheit.[32] Heating to this temperature, however, will not destroy prions.

Because science still has not resolved the debate on whether the prion responsible for BSE and vCJD can pass from cattle to poultry to cattle to humans, the FDA should take the most precautionary approach and assure that poultry litter is banned from cattle feed.

3. Requiring Dedicated Facilities For Processing Prohibited Material Is The Only Effective Way To Prevent Cross-Contamination of Prohibited and Non-Prohibited Materials

The ban on feeding mammalian meat-and-bone meal to ruminants has been characterized as the "most important measure to prevent the spread of BSE within the cattle population."[33] Under the current FDA regulation, feed and feed ingredients for ruminant animals may be processed in a facility that also processes prohibited proteins, although the rule requires that those firms handling both prohibited and non-prohibited material must have a system and a written plan to prevent cross-contamination.

In the Advanced Notice of Proposed Rulemaking, the FDA noted that both the Harvard risk assessment and the FDA public meeting identified cross-contamination of feed as a possible BSE risk. According to the FDA's Center for Veterinary Medicine's most recent compliance report, approximately 2% of renderers are still out of compliance with some aspect of the rule, including the requirement to have an adequate system in place to prevent co-mingling of

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[32] North Carolina Cooperative Extension Service, *Deep Stacking Broiler Litter as a Feed for Beef Cattle*, Publication Number AG-515-2 (Apr. 1995), available at *<http://www.ces.ncsu.edu/drought/dro-49.html>*.

[33] Center for Veterinary Medicine, Vol XVII, FDA Veterinarian, *The Spread of BSE in Switzerland - Epidemiology and Ongoing Eradication of a Challenging Disease* (Sept./Oct. 2002), at p. 6.

prohibited and non-prohibited material for use in ruminant feed.[34] For feed mills not licensed by the FDA, approximately 7% (representing 86 firms) of those subject to initial or follow-up inspection are still out of compliance with one or more aspects of the feed ban rule.[35] Because these data do not reveal the size of the firm cited or the volume of prohibited material handled, the scope of ongoing violations is unclear.

These ongoing violations – years following implementation of the feed ban – clearly indicate that the FDA's campaign to educate all sectors of the animal feed industry on the requirements of the rule still have failed to achieve full compliance, and that many firms handling prohibited material do not maintain separation of prohibited and non-prohibited material.

In addition, the General Accounting Office has found serious deficiencies in the FDA's enforcement strategy for feed ban compliance, including a lack of hierarchy of enforcement actions, criteria for actions to be taken, time frames for firms to correct violations and time frames for follow-up inspections to confirm that violations have been corrected.[36]

As long as prohibited and non-prohibited materials are processed and handled in the same facility, the potential for cross-contamination exists. The same potential for cross-contamination also exists with respect to the transportation of animal feed containing prohibited mammalian protein. Accordingly, the FDA should require separate, dedicated feed processing and handling

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[34] FDA, Center for Veterinary Medicine, 2002 CVM Update, *Ruminant Feed (BSE) Enforcement Activities* (Apr. 15, 2002). The volume of product processed by the out-of-compliance facilities is not known [hereinafter CVM, *Ruminant Feed (BSE) Enforcement Activities*].

[35] CVM, *Ruminant Feed (BSE) Enforcement Activities*, at p. 3.

[36] General Accounting Office, Report to Congressional Requesters, *Mad Cow Disease: Improvements in the Animal Feed Ban and Other Regulatory Areas Would Strengthen U.S. Prevention Efforts*, GAO-02-183 (Jan. 2002), at p. 24.

plants for the production and handling of ruminant feeds, as well as the dedicated transportation of animal feed containing prohibited mammalian protein, to avoid the risks of cross-contamination.

The FDA also has asked whether there are practical ways to prevent cross-contamination other than requiring complete separation. While FDA guidance recommends that firms processing and handling both prohibited and non-prohibited material have systems in place to prevent commingling, it does not require that these systems be validated to prevent cross-contamination. At a minimum, the agency should require firms, including transporters, to validate, using scientific tests, that their clean-out and flushing procedures are actually working to prevent cross-contamination and accidental mixing. This validation should be fully available to the government upon inspection.

FDA also should consider requiring firms to conduct ongoing verification demonstrating that their systems to prevent commingling are working properly. This should include a requirement for testing every batch of ruminant feed to confirm that it is free of protein derived from mammals and that there has been no unintentional mixing or cross-contamination.[37]

CONCLUSION

If the goal is to prevent the potential exposure of Americans to TSE agents, including BSE, from the animal and human food chain, then at a minimum the FDA should prohibit in the rendering process the use of SRMs from cattle twelve months and older, as well as SRMs from

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[37] The FDA has recently released a Notice of Proposed Rulemaking to implement the registration provisions of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. Among other things, owners, operators or agents in charge of domestic or foreign facilities that manufacture, process, pack or hold food for human or animal consumption in the United States would be required to register the facility with the FDA. Accordingly, feed mills would be required to register. Registration of feed mills is a step in the right direction since it is the only way the FDA can assure that it has an accurate count of such mills and that each mill is subject to inspection for compliance with the feed ban.

all ruminant wildlife and dead or downer animal stock. In addition, the FDA should implement a ban on the use of poultry litter in ruminant feed and require dedicated facilities for the processing, handling and transportation of animal feed containing prohibited materials.

Respectfully submitted,

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CSPI CENTER FOR SCIENCE IN THE PUBLIC INTEREST
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January 30, 2003

Dockets Management Branch (HFA-305)
Docket No. 02N-0273
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir or Madam:

Enclosed please find the original and two copies of CSPI's comments on the Advanced Notice of Proposed Rulemaking on Substances Prohibited From Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed. Please file these comments under Docket No. 02N-0273. Thank you very much.

Sincerely,

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