

August 13, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket No: 2004N-0081

Dear Sir or Madame:

As scientists and recognized experts who have worked in the field of TSEs for decades, we are deeply concerned by the recent discoveries of indigenous BSE infected cattle in North America and appreciate the opportunity to submit comments to this very important Advance Notice of Proposed Rulemaking (ANPRM). 69 Fed. Reg. 42288 (July 14, 2004).

We hope that the discovery of these indigenous cases will at last provide the necessary impetus to implement, monitor and enforce a comprehensive and protective feed ban that is more congruent with the measures that have been proven to be effective in the United Kingdom. The currently implemented ban in the UK evolved in response to repeated disappointments in predicted downturns in the epidemic course. The feed ban was implemented in 1988 followed by a specified bovine offals (SBO) ban two years later. The epidemic peaked two years after that but lingered much longer than anticipated. To bring it fully under control required increasingly inclusive bans and much more stringent enforcement. Inspired and justified by the appearance of the first human cases and the looming threat of a vCJD epidemic, beginning in 1996 there was an extension of the SBO ban to "specified risk materials", SRMs; implementation of the OTM scheme in which cattle over thirty months of age are placed in a higher risk category; and gradual extensions of the feed ban to all mammals and then all vertebrates and finally all feed uses. The change in enforcement in 1996 is readily evident in the epidemic record giving rise to the term BARBs, "Born After the Real Ban" in UK scientific circles. We in North America could do this experiment all over again, waiting for each new warning before adding more stringency to our control measures, or we can benefit from the British experience and take decisive measures now to arrest any further development of the underlying epidemic that is implicit in the two BSE cases discovered to date.

Hopefully, the cases that have currently come to light in North America represent the peak of whatever epidemic was incubating at the time that our own feed bans were implemented in 1998. If the bans (US and Canada) were effective, and the epidemic progressed similarly to that in the UK, we would expect a peak in 2004. However, if the bans have not been effective, either due to its exclusions, limited scope, or inadequate enforcement, the epidemic could still be growing.

There is no way to distinguish these two possibilities from the currently available data. The only way to obtain this data is through a much more comprehensive testing program than that proposed by the USDA, one designed specifically to establish the current prevalence of infected animals. (We recognize that a comprehensive program of this sort would also have ancillary benefits as a screening test for food.) Since we hope that the prevalence rates are low and stay low, we do not see how this can be accomplished credibly without universal testing. Without sound data on the actual prevalence of the infection it will not be possible to track the effectiveness of any control measures that are implemented. If the control measures are not effective it will eventually become apparent in the appearance of increasing numbers of new cases. However, the UK epidemic has taught us that by the time a BSE epidemic becomes readily apparent there are already a large cohort of infected individuals, large numbers of humans have already been put at risk, and it becomes increasingly difficult to control.

To guarantee our safety, it is essential that the North American bans provide absolute controls for specified risk materials (SRMs) by eliminating existing exemptions; by eliminating dead ruminant livestock as a source of animal feed; and by providing for greater control over cross contamination of ruminant feed by ruminant protein.

With SRM exemptions providing a source of infectivity to the animal feed system, the current US feed ban, still allows the possibility for cattle to be exposed to BSE through:

1. Feeding of ruminant protein back to ruminants per legal exemptions (*e.g.*, poultry litter, plate waste)
2. Cross feeding (the feeding of non-ruminant rations to ruminants) on farms
3. Cross contamination of ruminant and non-ruminant feed

In addition, there are other species which are susceptible to BSE and the regulations allow for SRMs to still be included in feed for these animals.

Hence we believe that FDA must assure that all possible sources of contaminated materials are fully removed from all animal feeds and that legal exemptions which allow ruminant protein to be fed back to ruminants (with the exception of milk) should be discontinued.<sup>1</sup>

## **SRMs**

Because infectivity studies are logistically challenging and expensive not every tissue on the SRM list has been bioassayed. The SRMs included in the USDA regulation, are tissues known to contain infectivity or to be closely associated with tissues known to contain infectivity. For example, the skull and vertebral column which encase the brain

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<sup>1</sup> Milk has not been a significant source of transmission of BSE in cattle.

and spinal cord, respectively, can be assumed to have gross contamination. The tissue distribution of infectivity in BSE infected cattle has primarily been determined by 3 studies conducted in the United Kingdom all of which had serious limitations.

In two of the studies bioassays were done in mice which are at least 1000 fold less sensitive to BSE than cattle themselves. Only the high titers of infectivity can be detected by this method. These investigations found infectivity in the brain and central nervous system as expected but also in the distal ileum of experimentally infected calves beginning only six months after challenge and continuing throughout life. (Wells et. al., 1994; 1998). Positive immunostaining for PrP<sup>tes</sup> was identified along the length of the intestine providing evidence that the entire intestine should be considered as SRM consistent with EU regulations (personal communication Danny Matthews, UK, VLA). We also note that the International Advisory Committee appointed by Secretary Veneman also recommended that the SRM ban in the US be amended to include the entire intestine from duodenum to rectum. Studies bioassayed in calves where sensitivity of the assay should be high has produced similar results and in addition found infectivity in tonsil and bone marrow and the lymphoid tissue of third eyelid (Dr. Danny Matthews, UK DEFRA, personal communication).

While bioassay in cattle is far preferable to mice in terms of sensitivity, cattle nevertheless present their own limitations in terms of the long incubation time (four to six years for high titer inoculum, and >10 to 12 years for low titer inoculations) and the limited number of animals that can be used for assay compared to rodents. As a consequence the significance of the negative finding for many tissues is questionable. For example, while muscle produced no infections, only 0.5g of muscle was bioassayed from a total of 1500 kg (Gerald Wells, UK DEFRA personal communication). In contrast, three recent reports have found either TSE infectivity or PrP amyloid in the muscles of sheep and rodents. In contrast with humans, sheep, monkeys, mice and hamsters, no infectivity was found in the blood of BSE infected cattle. We consider it very unlikely that cattle are the sole outlier to what has been a consistent finding in all other TSE diseases where the measurement has been made with sufficient sensitivity to detect the low levels of infectivity that are present in blood. Rather this failure is more likely a measure of the lack of sensitivity of the experimental methods of measurement. If blood is infected then all vascularized tissues can be expected to contain some infectivity in proportion to the content of residual blood. Certainly, blood and blood proteins should not be used as feed without conclusive evidence that they are safe.

### **Specific Exemptions to the feed ban that should be eliminated**

#### Poultry Litter

There are two sources of risk from poultry litter. Poultry litter not only consists of digested feed but also of feed which spills from the cages. As a consequence, the practice of feeding litter back to cattle is by its nature non-compliant with the current feed ban if the poultry themselves are being fed ruminant protein. Poultry traditionally consumed a large proportion of the MBM produced in the US. Given that ruminant

protein can no longer be fed to ruminants in the US and that most if not all countries will no longer import our ruminant MBM, an even larger part of poultry diets is now ruminant MBM. Spillage provides a direct link to back to cattle.

There is also no reason to expect that TSE infectivity would be inactivated by passage through the poultry gut, and only a dim possibility that it would be inactivated by composting. Thus the poultry feces are another potential route of transmission back to cattle. Evidence for this comes from rodent experiments where infectivity was demonstrated in the feces after being fed: “Laboratory experiments (Dickinson et al) show that mice orally challenged with scrapie have detectable infectivity that passes through the gut. Gut contents and fecal matter may therefore contain infectivity, and it is noted that in experimental oral challenges in cattle conducted in the UK, feces must be treated as medical waste for one month following the challenge. It is concluded that digestive contents and fecal material from livestock or poultry currently being fed with MBM potentially contaminated with BSE should not be used as a feed ingredient for animal feed.” **[Proceedings: Joint WHO/FAO/OIE/ Technical Consultation on BSE: public health, animal health and trade. Paris, 10-14 June 2001.**

It may be possible to remove the risk from poultry litter by sterilization. However, unless or until a method can be developed and validated, poultry litter should be banned from ruminant feed.

### Plate Waste

Plate waste is not limited to meat (muscle tissue). For example, cuts that include a portion of the spinal cord or that are contaminated by cord or ganglia during preparation could contain high levels of infectivity if derived from a TSE infected animal late in the preclinical stage of infection. At best this material would only be exposed to normal cooking temperatures. USDA, APHIS experience with the Swine Health Protection Act has revealed that plate waste also includes uncooked trimmings and bones. Although the current FDA regulation requires the plate waste be treated again, there are no specifications which would render a TSE agent inactive. Of greatest risk would be bovine sources of infectivity but sheep scrapie, although not known to be a risk for human consumption, is one of the possible origins of BSE. The sheep scrapie agent is known to be widely dispersed including relatively high titers in lymphoid as well as nervous tissue. We support the USDA’s opposition to the exemption of “plate waste” as stated in written comments since 1997.

### Ruminant Blood

As discussed above, we consider likely that the blood of BSE infected cattle contains low levels of infectivity similar to those found in humans, monkeys, sheep, mice and hamsters including sheep and mice infected with BSE. However, there is another, perhaps even more dangerous source of blood-borne infectivity in slaughtered cattle carrying the infection. This is because stunning releases micro emboli of brain tissue into the circulatory system where they become

widely distributed in the few moments before the exsanguination and death. (Anil et al, 1999; Anil, et al, 2001a & b; Anil et al, 2002; Love, et al, 2000; Mackey and Derrick, 1979) The risks from this source of infection extend really to all tissues in the body including those that end up as food and plate waste and as a consequence this issue has profound implications for public health as well as bovine health. It also impacts the significance and rationale for SRM and clearly needs to be understood far better than it is at present to be fully accounted for in a science based policy. This may be a special problem where sprayed dried blood is being used as a milk replacer for calves. The infection might never be seen in veal calves where this practice is most common, but could nevertheless amplify the spread the disease through other loop holes in the ban like plate waste. It is thought that young animals are especially susceptible to infection.

### Unfiltered Tallow

Ruminant tallow is exempted from the current feed ban. Tallow contains protein impurities (i.e. MBM) that could be a source of TSE infectivity. There are no FDA impurity level requirements for this tallow. It has been reported that it is standard practice to produce tallow which has an impurity level of .15% or below. However, it is not clear that this is adequate to remove the risk of transmission and there is no requirement to meet even this standard.

### **Risk from Deadstock**

The levels of total infectivity in a TSE infected animal increase as the animal approaches and progresses to clinical disease and infected individuals only exhibit recognizable clinical symptoms once infectivity titers have reached high levels in the brain. Surveillance data collected throughout Europe indicates there is a much greater likelihood for BSE to be detected in dead or down cattle than from healthy normal animals. An animal which dies of BSE would be at the peak of infectivity, that is they would carry the greatest amount of agent at this point in the disease.

In the 2001 Harvard risk assessment model it was shown that eliminating dead and downer, 4D cattle, from the feed stream was a disproportionately effective means of reducing the risk of reinfection. We endorse this approach and strongly recommend provisions to eliminate this source of exposure from ruminant feed. (Harvard Risk Assessment, 2001 Executive Summary)

### **Exposure: Cross Feeding and Cross Contamination**

The UK epidemiology has clearly shown that BSE contaminated feed is the primary if not sole vehicle for the transmission of BSE between cattle. Moreover, results from the United Kingdom's attack rate study indicate that it does not take much exposure to transmit BSE to cattle. Recent results from the attack rate study which is still in progress has found that .1 gr of brain transmitted BSE to 3 cows out of 15 thus far, and .01 and .001gr of brain has transmitted BSE (1 cow out of 15). (Danny Matthews, DEFRA presentation at TAFS meeting, Washington, DC April 2004).

Rendering may reduce infectivity but it does not eliminate it. (Taylor et al, 1995; Taylor et al, 1997; Schreuder et al, 1998). Given that BSE can be transmitted to cattle via an oral route with just .001 gram of infected tissue, it does not take much infectivity to contaminate feed and keep the disease recycling. This is especially true in the US and other countries which do not have dedicated lines and equipment to manufacture and process feed for ruminants and non ruminants.

In addition, epidemiological investigations in European countries have shown that cross feeding and cross contamination on farm can be a significant vehicle for continued BSE transmission even after feed bans are well established. Cross feeding is the inadvertent practice of feeding meal for poultry or pigs (which has a likelihood of being ruminant MBM) to cattle on the same farm. This is usually due to simple human error. (Hoinville, 1994; Hoinville et al, 1995; Doherr et al, 2002a; Stevenson et al, 2000)

FDA, CVM reports that compliance with the feed ban is over 90%. For the most part this does not include the compliance level on the farm. There are hundreds of thousands of farms in the US. Many of these have multiple species. That is they have cattle, pigs, chickens etc. The sheer numbers of farms make it very difficult to assure compliance on farm and to adequately cover all farms by inspection. The rendering industry and feed industry can maintain 100% compliance at their facilities but if a producer inadvertently feeds chicken feed to cattle the compliance rate higher in the chain is negated.

The May 2003 Canadian BSE case illustrates the possibility of these mistakes. The positive cow was rendered and then MBM distributed to various locations. Two of these locations included poultry farms which mixed their own feed. The farms also had cattle. The investigation could not eliminate the possibility that the cattle were fed the same feed as the poultry. The cattle on these farms were completely depopulated.

Human error is extremely difficult to prevent especially when enforcement has extreme logistical challenges. By eliminating all material (SRMs and deadstock) which may introduce infectivity into the system before any processing, the resulting MBM becomes inherently safer. If mistakes are then made on farm, they become much less relevant in regards to the recycling of BSE.

## **Exposure: Susceptibility of other Species**

### **Felines**

A transmissible spongiform encephalopathy has been diagnosed in eight species of captive wild ruminants as well as exotic (cheetahs, pumas, a tiger and an ocelot) and domestic cats. There have been over 80 domestic cat cases of Feline Spongiform Encephalopathy (FSE) in Great Britain, and cats in Norway, Northern Ireland, Lichtenstein and Switzerland. The agent isolated from several of these cases is indistinguishable from BSE in cattle using strain typing in mice, suggesting that FSE is actually BSE in exotic and domestic cats. This also appears to be true for

the other ruminants. Epidemiological evidence suggests BSE contaminated feed to be the primary source of infection in these species. (MAFF Progress Report, June 1997), thus providing additional supporting evidence for the dangers of BSE contaminated feed the necessity of removing all sources of potential contamination from the feed stream.

### **Other species**

Studies conducted at the National Institutes of Health Rocky Mountain Laboratory caution against assuming that animals which do not become clinically ill are not infected. It is unknown if certain animals may become carriers, i.e., become infected, shed agent but do not progress to develop clinical disease. Infection of certain rodent species with different TSE strains suggests the possibility of a carrier state (Collis and Kimberlin 1985; Race and Chesebro, 1998; Race et. al, 2001). In the most recent study, mice were inoculated with 263K hamster scrapie. There was a prolonged period (approximately one year) where there was no evidence of replication of infectivity. Furthermore, there was no evidence of PrPSc during this phase of inactive persistence. This study found that this phase was followed by a period of active replication of infectivity and agent adaptation. In most cases, PrPSc was not detected in the active phase as well (Race et. al., 2001). It is important to determine if this persistence and adaptation occurs in other species exposed to TSEs as it may have significance in feeding programs which continually expose certain species to BSE infectivity. For example, if BSE infected brain and spinal cord are continually fed to certain species, it may be possible for the agent to persist and adapt in these new species. Over time, the 'resistant' species may become a source of agent. Considering the results of the study by Race and colleagues, if there were an inactive persistence phase in certain species, PrP Sc would not be detectable, yet there would be infectivity (Race et. al., 2001).

Pigs displayed evidence of a TSE after exposure to BSE by 3 parenteral routes(Dawson et. al., 1990). In this transmission there was evidence of infectivity in the CNS, stomach, intestine and pancreas of the pigs. Oral transmission has been attempted in swine. The inoculated swine were euthanized after 84 months of age and had not exhibited any signs of a TSE. Parenteral and oral transmission has also been attempted in chickens with no evidence of disease. Tissues from the BSE-challenged pigs and chickens were inoculated into susceptible mice to look for residual infectivity, to date none has been found. The criticism of this study is the use of mice instead of cattle as the assay model due to the decrease of sensitivity.

If any of these scenarios became established in commercial species they could become reservoirs for reinfection of cattle and perpetuation or reintroduction of the epidemic. We offer these possibilities to reinforce the need to eliminate all possible sources of contamination from the feed stream.

The need to remove high risk material from all animal feed is also supported by other bodies with expertise in the field of TSEs:

### Recommendations of the World Health Organization (WHO)

The World Health Organization (WHO) has issued the following recommendations for countries with BSE or those where a known exposure exists:

- No part or product of any animal which has shown signs of a TSE should enter any food chain (human or animal). In particular:
  - All countries must ensure the killing and safe disposal of all parts or products of such animals so that TSE infectivity cannot enter any food chain.
  - Countries should not permit tissues that are likely to contain the BSE agent to enter any food chain (human or animal).

From the report of a WHO Consultation on Public Health Issues related to Human and Animal Transmissible Spongiform Encephalopathies WHO/EMC/DIS 96.147, Geneva, 2-3 April 1996.

#### Recommendations of the Harvard/Tuskegee BSE Risk Assessment

Executive Summary of the 2001 release:

*“Specific pathways or practices that would contribute the most to the spread of BSE if it were introduced into the U.S. relate to compliance with the FDA feed ban and include misfeeding on the farm and the mislabeling of feed and feed products prohibited for consumption by cattle. The disposition of cattle that die on the farm would also have a substantial influence on the spread of BSE if this disease were introduced into the U.S.”*

*“Our evaluation of potential risk mitigation actions highlights potential measures to further reduce the already low likelihood that BSE could spread to cattle or contaminate human food if it were to arise. Prohibiting the rendering of animals that die on the farm, possibly of BSE, removes a great deal of potential contamination in the animal feed chain and reduces average predicted cases of BSE following introduction of ten infected cattle by 77%. Implementation of a UK-style ban on specified risk material (e.g., spinal cords, brains, vertebral columns) from both human food and animal feed reduces the predicted number of BSE cases in cattle by 80% and the potential human exposure by 95%.”*

*“The disposition of cattle that die on the farm would also have a substantial influence on the spread of BSE if the disease were introduced.” The base case scenario showed that the mean total number of ID50s (i.e., dosage sufficient to infect 50 percent of exposed cattle) from healthy animals at slaughter presented to the food/feed system was 1500. The mean total number of ID50s from adult cattle deadstock presented to the feed system was 37,000. This illustrates the risk of “4D cattle” (i.e., deadstock). From the Harvard Risk Assessment, 2001, Appendix 3A Base Case.*

#### Recommendations of the Subcommittee to the USDA’s Foreign Animal and Poultry Disease Advisory Committee

An international panel of transmissible spongiform encephalopathy (TSE) experts appointed by Secretary of Agriculture Ann M. Veneman as a subcommittee to the Foreign Animal and Poultry Disease Advisory Committee issued a report in February 2004 which stated:

*“... given the epidemiological evidence indicating that BSE agent was already circulating in ruminant feed prior to the feed ban in 1997, and the integration of the North American cattle and feed industries, strong consideration should be given to excluding all SRM from both the human food and animal feed supplies.”*

*“Considering the BSE situation in North America, the subcommittee believes the partial (ruminant to ruminant) feed ban that is currently in place is insufficient to prevent exposure of cattle to the BSE agent.”*

From the Secretary’s Advisory Committee on Foreign Animal and Poultry Diseases’ Subcommittee on the United States’ Response to the Detection of a Case of Bovine Spongiform Encephalopathy, Report on Measures Relating to Bovine Spongiform Encephalopathy (BSE) in the United States, 2 February 2004, p. 8.

## **Conclusion**

In conclusion we urge the FDA to implement, monitor and enforce a comprehensive and protective feed ban that is more congruent with the measures that have been proven to be effective in the United Kingdom. We do not feel that we can overstate the dangers from the insidious threat from these diseases and the need to control and arrest them before the spread widely.

However we also wish to emphasize that as scientists that have dedicated substantive portions of our careers to defining the risks from TSEs as well as developing strategies for managing those risks, we are confident that there will eventually be technical solutions to many of the challenges that we currently confront from these diseases. Thus, we urge the FDA to frame its regulations in terms that allow for the use of any banned material if it can be proven safe for a given application.

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