

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-0264

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 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 throughout Europe. The currently implemented ban in the UK evolved in response to repeated disappointments in predicted downturns in the epidemic course. The initial 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 feed bans extending first to all mammals and then all animal protein and beginning in 1996 much more stringent enforcement. The change 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 experience of others and take decisive measures now to arrest the further development of underlying cases that is implicit in the two already discovered to date.

Hopefully, the cases that have currently come to light in North America represent the peak of whatever outbreak was incubating at the time that our own feed bans were implemented in 1997. If the bans (US and Canada) were effective, and the disease manifestation progressed similarly to that in the UK and other countries, we would expect to be past the peak of cases. However, if the bans have not been effective, either due to its exclusions, limited scope, or inadequate enforcement, the agent could still be recycling.

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

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which extends over a period of time. If the control measures are not effective it will eventually become apparent in the appearance of increasing numbers of new cases. However, the UK and Swiss experiences have taught us that by the time a BSE outbreak becomes readily apparent there is already a larger cohort of infected cattle. That is, a country does not see the success or failure of measures until 5-6 years post implementation.

Hence, it is essential that the North American bans provide strict controls for specified risk materials (SRMs) eliminate existing exemptions; eliminate dead ruminant livestock as a source of animal feed; and provide 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 be included in feed for these animals.

For BSE to be perpetuated, the animal production system must have a source of agent and a means by which cattle or other susceptible species are exposed to this agent. We feel that in the United States, the source and routes of exposure still exist, hence allowing for the continued recycling of BSE. We believe that FDA must assure that all possible sources of contaminated materials (SRMs and ruminant deadstock) 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.¹

Risk from 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 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 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 higher titers of infectivity can be detected

¹ To date milk has not been shown to be a source of transmission of BSE in cattle.

by this method. These investigations found infectivity in the brain, spinal cord, retina, trigeminal ganglia, dorsal root ganglia, distal ileum and bone marrow (the bone marrow finding was from one animal). Infectivity was found in distal ileum of experimentally infected calves beginning six months after challenge and continuing at other intervals throughout life. (Wells et. al., 1994; 1998). Positive immunostaining for PrP^{res} was identified along the length of the intestine providing evidence that the entire intestine should be considered as SRM (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. The bioassay study in calves has produced similar results and in addition infectivity has been found in tonsil. The study is still in progress. Another project has found infectivity in the lymphoid tissue of third eyelid from naturally infected animals. (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.

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 all animal feed. (Harvard Risk Assessment, 2001 Executive Summary)

Exposure: 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 slim possibility that composting would reduce infectivity at all. 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 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; and Alan Dickinson, personal communication].

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 any bovine source of infectivity but also 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

In contrast with humans, sheep, monkeys, mice and hamsters, including sheep and mice infected with BSE and humans infected with vCJD considered identical to BSE, no infectivity has so far been demonstrated in the blood of BSE infected cattle. However, we consider it 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.

Micro emboli are another possible source of blood-borne agent in slaughtered cattle carrying BSE infection. Stunning can release micro emboli of brain tissue into the circulatory system from where they can be distributed to other tissues in the few moments before the exsanguination and death. (Anil, et al, 2001a & b; Anil et al, 2002; Love, et al, 2000). This source of infection could extend a higher infectivity risk to tissues that would otherwise be at low risk allowing exposure of cattle through any of the legal exemptions potentially producing a feed and food risk. It 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. Blood-borne infectivity may be a special problem where sprayed dried blood is being used as a milk replacer for calves, as it is thought that young animals are especially susceptible to infection.

Certainly, blood and blood proteins should not be used as feed without conclusive evidence that they are safe.

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, but it is not clear that this is fully adequate to remove the risk of transmission and there is no requirement to meet even this standard.

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 g of brain transmitted BSE to 3 cows out of 15 thus far, and .01 and .001 gr 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 there 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 (Wyatt 1991). 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. 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 and reinforcing 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 (Race and Chesebro, 1998; Race et. al, 2001, Race et al., 2002). In the more recent studies, 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 PrPres during this phase of inactive persistence, which was followed by a period of active replication of infectivity and agent adaptation. In most cases, PrPres was not detected in the active phase as well. 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 other 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. The results of Race and colleagues, warns that an inactive persistent phase might not be produce detectable PrPres, yet there would be infectivity (Race et. al., 2001).

Pigs displayed evidence of a TSE after exposure to BSE by 3 distinct parenteral routes, **with** evidence of infectivity in the CNS, stomach, intestine and pancreas of the pigs (Dawson et. al., 1990). Oral transmission has also been attempted in swine, but after an observation period of 84 months there was neither clinical nor pathological evidence of infection (Dawson et. al., 1990). 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, but to date none has been found. In both instances the detection sensitivity was limited by the use of mice for bioassay instead of same species transmissions into cattle (or pigs and chickens).

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 infectivity 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 other countries which have experienced BSE. 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 future use of any banned material if it can be proven safe for a given application.

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