Scientific Status Summary

Transmissible Spongiform Encephalopathies

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The Institute of Food Technologists has issued this Scientific Status Summary to update our knowledge of transmissible spongiform encephalopathies and provide an authoritative perspective on the surrounding regulatory and trade landscape.

Keywords: Scrapie, Chronic Wasting Disease, Bovine Spongiform Encephalopathy, Creutzfeldt-Jakob disease

Transmissible spongiform encephalopathies (TSEs) encompass a group of diseases affecting several mammalian species—mink, cats, sheep, goats, cattle, deer, and elk (Figure 1)—including humans. These diseases are *transmissible* because they are capable of being transferred from one animal to another, *spongiform* because they cause the appearance of sponge-like holes in the brain of those affected, and *encephalopathic* because they are neurodegenerative diseases of the brain.

TSEs continue to pose a concern with respect to animal and human health. This was recently underscored by discovery of bovine spongiform encephalopathy (BSE)–positive cattle in Canada and the United States and the apparent spread of variant Creutzfeldt-Jakob Disease (vCJD) in humans through blood transfusions. The TSE threat to humans can be attributed to the fact that there are direct and indirect routes of exposure. As a result, the U.S. government, including the U.S. Dept. of Agriculture, the Food and Drug Administration, and the Environmental Protection Agency, is being called on to develop the regulatory framework necessary to protect the public, the animals, and the environment.

From an economic perspective, TSEs have brought about trade disruption and additional processing requirements resulting in hardship for cattle producers, meat processors, feed manufacturers, and renderers. The impacts include changes in slaughtering and deboning techniques, implementation of special handling procedures for specified risk materials (SRMs), additional labeling requirements, and significant disposal and waste-handling challenges for the industry.

From a government perspective, TSEs have created a need for increased regulation and monitoring of meat processing and rendering facilities, with resultant effects on the food and feed industries (for example, ingredients derived from edible rendering, including fats, oils, and emulsifiers).

Summarizing the scientific, regulatory, and trade landscape of TSEs has proven to be quite a challenge because of the constantly evolving information pertaining to these diseases. This Scientific Status Summary attempts to capture major findings and trends, and we encourage the reader to check for updates, as new research may alter our current understanding.

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Science Review

The first evidence of TSE diagnosis was recorded in Europe in sheep in 1732 (DEFRA 2002), although the disease was not recognized to be transmissible until 1936 (Cuille and Chelle 1936). TSEs cause brain vacuolation, astrogliosis, neuronal apoptosis, and accumulation of misfolded, protease-resistant prion proteins in the central nervous system (Soto and Castilla 2004). As a result, affected animals or people develop varied neurologic symptoms. Victims do not display a classic immune response, and there is no treatment. Table 1 provides an overview of disease characteristics pertaining to the TSEs reviewed in this report.

Transmission of TSEs is a complex and active area of research. Some TSEs are not contagious (BSE) but can be transmitted orally, for example, spread through contaminated feed, while others (scrapie and chronic wasting disease, CWD) are contagious and thought to be spread more easily, for example, via contact with placenta and placental fluids or environmental contamination. Still other TSEs are spontaneous (classical CJD) or hereditary (Gerstmann-Strausler-Sheinker disease, GSS), and several TSEs can be spread through tissue transplantation (Brown 2003). The agent of transmission is known as a prion—an abnormally shaped protein lacking nucleic acid that was isolated and named in 1982 by Stanley B. Prusiner. The word "prion" is derived from "**pro**teinaceous **in**fectious particle" (Prusiner 1982). Prusiner and his group were able to ascertain the genetic code for the prion protein (PrP) and demonstrate that its mRNA is a product of a single host gene. This gene is present in the brain of disease-free animals and constitutively expressed by many cell types. The prion protein exists in two forms, normal (PrP^{c}) and its pathological isoform (PrP^{res}); the latter is extremely hardy, resists protease digestion and survives dry heat for 15 minutes at 600 °C (Prusiner 1998; Brown and others 2000). The differences between PrP^{c} and PrP^{res} lie in their tertiary (three-dimensional) structure (Figure 2) that arises due to a shift from α-helix (PrP^{c}) to β-pleated sheet (PrP^{res}) (Soto and Castilla 2004).

The origin of pathological prions is not fully understood, sparking debate among those who study this disease family. Some believe

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that these infective prions originated in one species and then were passed to other animals, while others think they spontaneously arose in each species independently (Brown 2001).

For an animal to acquire a TSE, PrP^{c} must be a part of that animal's normal mammalian cells (Bueler and others 1993; Prusiner 1998). This protein is expressed most abundantly in the central nervous system (CNS) tissue and brain. Known TSEs are associated with a structural malformation of this protein that alters its function and results in cell damage. Microscopic spongiform lesions form in defined regions of the brain, resulting in nervous system dysfunction and eventual death (Brown and others 2000). Within the same species, the genetics of the host often determines predisposition to this malformation (misfolding), with some genotypes being more or less susceptible. Researchers have determined that change (polymorphism) in only 1 to 3 base-pairs of the gene that encodes the normal prion protein can change resistance to prion disease for sheep, elk, and humans (Cross and Burmester 2002). Genetic differences among these diseases are outlined in Table 2.

TSEs are inhibited—to varying degrees—from spreading from one species to another by what is referred to as the "species barrier" (Bollinger and others 2004). Prion disease is initiated as abnormal prions (PrP^{res}) interact with normal prions (PrP^{c}) and precipi-

Table 1—Comparison of clinical aspects of the TSE diseases. Information is accurate to the best of our knowledge—new results continue to present.

	Scrapie	CWD	BSE	vCJD
Date, place of recognition	1732, UK	1967, USA	1986, UK	1996, UK
Species	Sheep/goats	Deer/elk	Ruminants/felines	Humans
Transmission	Lateral (direct) transmission via contact with placenta and fluids *Contagious*	Lateral (direct) transmission or environmental (indirect) *Contagious*	Ingestion of MBM derived from BSE-infected cattle *Non-contagious*	Consumption of BSE contaminated cattle materials or iatrogenic *Non-contagious*
Incubation time	2 to 5 y	1 to 3 y	4 to 5 y	10 to 15 y
Symptoms	Slight behavior change (nervous, aggressive, solitary) followed by itching and/or hypersensitivity, then motor abnormalities	Slight behavior change followed by repetitive behaviors, depression, then decreased appetite and weight loss, then increased urination, slobbering, and stumbling	Slight behavior change (nervous, reluctant to enter doorways, kick when milked), teeth grinding, frenzy, locomotor ataxia, hyperaesthesia, excessive licking, weight loss, low milk	Depression, anxiety, personality change followed by pain in limbs, face, body (tingling, numbness), then at 6 mo: clumsy, slurred speech, involuntary movements, and memory loss
Duration of illness	1 to 6 mo	2 to 3 mo	1 to 3 mo	12 to 18 mo
Minimum onset age	24 mo	<12 mo	22 mo	Adolescence
Methods of diagnosis	IHC[a], SAF-immunoblot of brain Live-animal test: biopsy of 3rd eyelid	IHC, SAF-immunoblot of brain, lymph nodes (neck), tonsils	IHC, SAF-immunoblot of brain (conclusive) Rapid screening methods (inconclusive)[b]: *Prionics WB* *Prionics LIA* *BioRad TeSeE* *Abbott/Enfer Test* *IDEXX HerdChek*	IHC, SAF-immunoblot of brain (conclusive) Other methods (inconclusive): MRI: increased signal in the thalmic region (90% of cases) EEG, spinal tap (14-3-3 protein)[c], tonsilar biopsy
Organs accumulating prion protein	CNS, spleen, lymph nodes, placenta, intestine (large and small), blood, pancreas, ovary, liver, muscle	Brain, pituitary, spinal cord, eyes, tonsils, lymph, spleen, pancreas, peripheral nerves	Brain, spinal cord, eyes, tonsils, trigeminal ganglia, dorsal root ganglion, distal ileum of the small intestine, 3rd eyelid	Brain, pituitary, spinal cord, eyes, tonsils, lymph nodes, spleen

[a]IHC = immunohistochemistry done using antibody/antigen staining of postmortem biopsy tissue.
[b]BSE rapid methods are USDA/APHIS approved for use as screening tests in the expanded surveillance program.
[c]From National Prion Disease Pathology Surveillance Center, www.cjdsurveillance.com/.

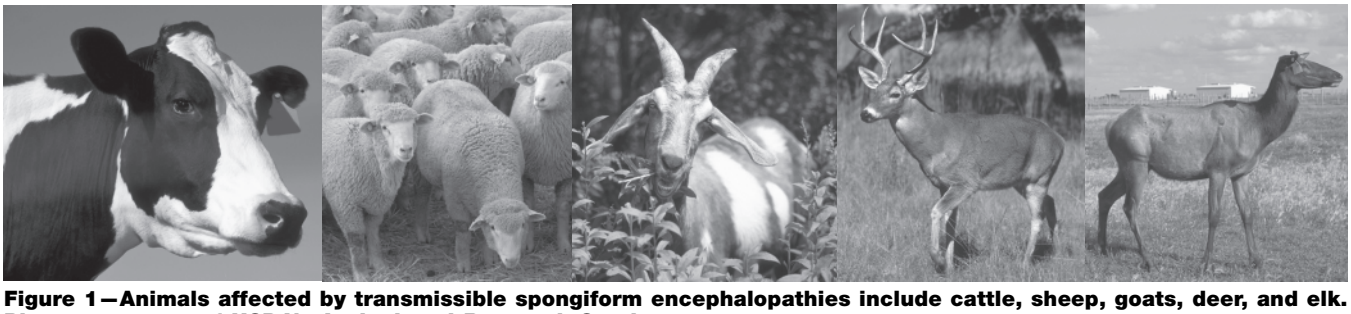

Figure 1—Animals affected by transmissible spongiform encephalopathies include cattle, sheep, goats, deer, and elk. Photos courtesy of USDA's Agricultural Research Service.

Table 2—Genetics and zoonotics of selected animal and human TSEs. Letters represent amino acids[a].

	Sheep scrapie	Deer and elk CWD	Cattle BSE	Human vCJD
Polymorphism codon(s) and code	171 Q/R/K/H[b]	White-tail deer: 95 Q/H, 96 G/S, 138 S/N[c] Mule deer: 20 D/G, 225 S/F[d] Elk: 132 M/L[e]	50–91, with 5 or 6 octapeptide repeats in the region[f]	129 M/V[f]
Susceptibility	High: QQ Low: RR[b]	White-tail deer: More QGS, less QSS = greater susceptibility[c] Mule deer: DS = greater susceptibility[d] Elk: MM = greater susceptibility [e]	Studies to date have shown no genetic indication of susceptibility	All clinical cases of vCJD to date have been MM[g]
Zoonotic?[h]	No	No	Yes	—
Cell-free human PrP conversion rate[i]	Intermediate (2 to 4 times weaker)	Low (5 to 12 times weaker)	Very low (>14 times weaker)	—

[a]A = alanine, D = aspartate, G = glycine, H = histidine, K = lysine, L = leucine, M = methionine, N = asparagine, Q = glutamine, R = arginine, S = serine, V = valine. Amino acid groups represent genotype combinations (each animal inherits a PrP gene from each parent).
[b]From APHIS (2003a). Note: Codons 136 and 154 are also indicators of susceptibility.
[c]From Johnson and others (2003).
[d]From Brayton and others (2004).
[e]From Cross and Burmester (2002).
[f]From Brown (2003).
[g]From Wadsworth and others (2004).
[h]Knowledge of TSEs is continuing to develop.
[i]From Raymond and others (2000). Note: Conversion rate based on inter-cervid conversion of prion proteins—it is a test of the molecular compatability between PrP^{c} and PrP^{res} of different sequences.

tate a shape change in the protein itself, a process called conversion. The species barrier is a function of the prion strain itself and degree of PrP sequence homology between donor infective prion and recipient prion. A greater species barrier for a given prion results in greater resistance for a recipient species animal and a longer incubation time from exposure to the onset of disease. Once the barrier has been crossed, incubation time decreases upon serial transmission (within species) due to increased PrP sequence homology (Prusiner 1998). In addition, as exposure dose increases, incubation time decreases, and vice versa. This is supported by United Kingdom epidemiological data that shows an increase in the age of the youngest case detected each year as the time since the implementation of feed regulations banning the practice of feeding mammalian meat-and-bone meal to cattle increases and the theoretical exposure dose has likewise declined (DEFRA 2005).

Each of the TSE diseases seems to be linked to multiple prion strains, each slightly different from the next and each causing slightly different symptoms. Until recently, BSE was thought to defy this phenomenon and stick to one strain; however, atypical cases in France and Italy have suggested that initial conclusions in this regard may have been erroneous. A new form of TSE in cattle has been deemed bovine amyloidotic spongiform encephalopathy (BASE). The molecular weight and distribution of the BASE protein within the brain differs from that of BSE—instead of granular, stringy deposits, BASE causes globular accumulations of tangled protein in the brain (that is, plaques). The discovery team found that BASE is similar in molecular structure to that of sporadic Creutzfeldt-Jakob Disease (CJD), one of the human forms of TSE, suggesting that it may not share the same origins as BSE (Casalone and others 2004).

The multi-strain phenomenon is considered by some to be a weak point in the prion hypothesis because such differences would be expected to arise from mutations or polymorphisms in the genetic material of the infectious agent; but in the case of TSEs, prion protein does not contain nucleic acids (Soto and Castilla 2004). Prusiner (1998) attributed the ability of prions to exist as different "strains" to slight differences in their conformation or aggregation states.

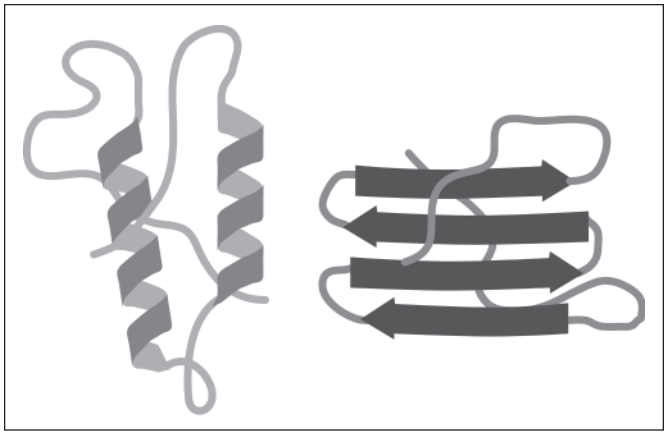

Figure 2—The agents responsible for TSEs are unique proteins called prions. The normal form becomes infectious when its three-dimensional structure changes from a normal α-helix (shown at left) to a misfolded β-pleated sheet, resulting in altered function, including the ability to damage cells. Illustration courtesy of Genetic Science Learning Center, Univ. of Utah, http://gslc.genetics.utah.edu.

Scrapie

Scrapie is generally thought to be the most widespread TSE disease, having inflicted thousands of sheep throughout the world, excluding New Zealand, Australia, and a few countries in South America (WHO 2002). Scrapie is transmitted from ewe to offspring and other lambs via contact with the placenta and its fluids. Clinical symptoms usually do not arise for 2 to 5 y, while death occurs within 1 to 6 mo following onset of such symptoms (Table 1) (APHIS 2004a). The infective agent accumulates in the lymphoreticular and peripheral nervous systems, where it may be detected within months of birth (Jeffrey and Gonzalez 2004).

Epidemiological studies to date have failed to demonstrate that scrapie can be transferred to humans; however, there is evidence suggesting that scrapie was transmitted to cattle and thereby initiated the European "mad cow" epidemic (Brown 2001). In 2000, the European Union instituted a ban on SRMs of both cattle and sheep from the animal and human food supply (European Community 2000), in part because of an inability to clinically distinguish between the symptoms of scrapie and those of BSE.

Genetic susceptibility of sheep to scrapie is determined by polymorphisms at codons 136 (valine or alanine) and 171 (glutamine, arginine, lysine, or histidine); codon 154 also plays a minor role in

susceptibility. Sheep homozygous for alanine at codon 136 and arginine at codon 171 (AARR) are almost completely resistant to scrapie. This genetic knowledge is being used to design breeding programs to control its spread (APHIS 2003a). USDA's Animal and Plant Health Inspection Service (APHIS) has initiated a Scrapie Eradication Program in the U.S. that consists of the following elements:

- Identification of preclinical infected sheep through live-animal testing and active slaughter surveillance.
- Effective tracking of infected animals to their flock/herd of origin, made possible as a result of identification requirements.
- Provision of effective genetic-based flock cleanup.

APHIS provides the following to exposed and infected flocks/herds that participate in cleanup or monitoring programs:

- Indemnity for high-risk, suspect, and scrapie-positive sheep and goats which owners agree to destroy.
- Scrapie live-animal testing.
- Genetic testing.
- Testing of exposed animals that have been sold out of infected and source flocks/herds (APHIS 2004a).

Chronic Wasting Disease

CWD is the only known TSE that appears to affect both free-ranging and captive species. The affected species include mule deer (*Odocoileus hemionus*), white-tailed deer (*Odocoileus virginianus*), and elk (*Cervus elaphus*). Available data suggest that CWD may be the rarest animal TSE, being diagnosed in only about 1000 deer and elk, with only 2 of those outside of North America (Miller and Williams 2004).

Endemic to Colorado and southern Wyoming (Miller and Williams 2004), CWD has also been identified in free-ranging cervids in Nebraska, New Mexico, South Dakota, Utah, Wisconsin, Illinois, and New York in the U.S. and Saskatchewan in Canada. However, due to limited surveillance efforts, the true prevalence and geographic spread remain unknown (Bollinger and others 2004).

Surveillance has demonstrated CWD transmission within the farmed cervid industry through trade of breeding stock. Farmed cervids found to be positive for CWD have been identified in Colorado, South Dakota, Minnesota, Montana, Kansas, Oklahoma, Nebraska, Wisconsin, and, most recently, New York. Elsewhere, the disease has been found in the Canadian provinces of Saskatchewan and Alberta, and even in Korea (an import from Canada).

Unlike scrapie, CWD does not appear to be transmitted vertically (mother to offspring) but rather is infectious and transferred horizontally from infected to susceptible individuals, possibly through shedding in feces and saliva (that is, direct contact and ingestion of abnormal prions) (Bollinger and others 2004). CWD has also been shown to be spread via residual infectivity from contaminated environments (Miller and others 2004). Cervid population density in Colorado and Wyoming is low, ranging between 2 and 5 animals per square kilometer (Bollinger and others 2004); therefore transmission of the disease in such regions is less likely than in higher-animal-density areas such as Wisconsin and Illinois. This fact, coupled with its ability to spread horizontally and endure in the environment for long periods of time, places increased emphasis on the potential for proliferation of the disease via the environment, making environmental contamination a cause for concern.

Like scrapie, CWD has no known zoonotic potential. In-vitro conversion experiments (Raymond and others 2000) indicate that CWD prions can convert human, cattle, and sheep prions to the abnormal form at very low rates; however, in-vivo studies have not shown transmission of the CWD infective agent to other animals, nor have epidemiological studies provided strong evidence for transmission to humans (Belay and others 2004; Bollinger and others 2004). Regardless, the American Veterinary Medical Association (AVMA 2004) and many state agriculture departments recommend that the following handling precautions be followed when dealing with game meat:

- Avoid harvesting deer or elk that appear sick.
- Wear rubber gloves while field dressing animals.
- Remove all bone and fatty tissue from the meat of animals.
- Minimize handling of the brain, spinal cord, spleen, tonsils, lymph nodes, and eyes.
- Avoid consuming tissue from any animal testing positive for CWD.
- Do not remove anything but pure meat (muscle) from areas where CWD is known to exist.

On December 24, 2003, APHIS issued a proposed rule to initiate a CWD Eradication Program (APHIS 2003b) with a goal of eliminating CWD from captive deer and elk herds. The proposed program consisted of identification, testing of adults dying or moving to slaughter, and herd management and control of animal movement into and out of herds. Once a herd has not been diagnosed with a case of CWD for 5 y, it would be "certified," indicating that it is low-risk for harboring the disease. The program has been undergoing final regulatory review and has yet to be implemented.

Bovine Spongiform Encephalopathy

BSE has been detected in more than 182000 cattle in more than 35000 different herds in the UK since it was first detected there in 1986, and in more than 3800 cattle in other countries throughout the world, including Canada and the U.S. (WHO 2002; European Union 2004). BSE is infectious and thought to be zoonotic but non-contagious because it is not excreted, thereby preventing horizontal transmission from cow to cow. It also fits the definition of a "production disease" because its transmission is dependent on feed management practices (Doherr 2003).

The origin of the first BSE case remains unverified, but transmission has been linked to feeding mammalian-derived proteins to cattle through established rendering practices (Denny and Hueston 1997; Brown and others 2001; WHO 2002). One popular theory holds that BSE originated from scrapie due to a high incidence of scrapie in the UK, combined with a very large number of sheep compared to cattle (4:1 ratio) and the fact that those animals were rendered together with cattle. Rendered proteins from sheep containing the scrapie infective agent would have then been fed to calves as young as a few days of age because of a relative lack of economical plant-derived protein supplements.

As a result of changes in rendering practices in the late 1970s, consolidation of the rendering and feed industries, and rapidly increasing sheep numbers, increased levels of scrapie (and BSE) infective agent would have survived the rendering process and been recycled to cattle as they were incorporated into cattle feeds (Brown 2001). Meat and bone meal (MBM) is a major by-product of rendering that, before discovery of BSE, was used extensively as a protein source in animal feed. Feeding MBM inadvertently served to amplify the BSE problem because rendering failed to completely inactivate the agent (WHO 2002). Also, upon feeding MBM back to cattle, the species barrier was removed, allowing less material to invoke greater numbers of infections (Brown 2001, 2003).

Abnormal BSE prions initially accumulate and are detected in the distal ileum, followed by the tonsils and then the central nervous system (brain and spinal cord) (European Union 2004). Table 3 shows the level of infectivity of affected tissues in a typical clinical case of BSE. No infective proteins have been found in muscle or milk samples from naturally occurring or experimentally challenged BSE cases (Brown 2001).

The European Experience

Beginning in December 1984, unusual behavior was noted among cattle on a farm in Sussex, U.K. Brain samples collected from one of those cattle were later recognized as a new disease (BSE) by Dr. Gerald Wells of the Consultant Pathology Unit at the Central Veterinary Laboratory in the UK (BSE Inquiry 2000). Undoubtedly, this was not the first case of BSE, although the infection appears to have been exceedingly rare before the early 1980s.

In 1988, the British government asked the Southwood Working Party (SWP) to advise on the risks posed by BSE and to develop recommendations to minimize or eliminate those risks. In an effort to protect animal health, on May 6 of that year William Rees, Chief Veterinary Officer of the UK, submitted a recommendation that mammalian material no longer be fed to ruminant animals based on initial epidemiologic studies of John Wilesmith (1988). This recommendation was supported by the SWP at its first meeting in June 1988, where the group decided on the following recommendations:

- Form a research group to analyze current research and develop research recommendations, especially in relation to transmissibility.
- Initiate testing to study the hypothesis that BSE arose because scrapie jumped the species barrier.
- Identify and follow the approximately 150 offspring of the known BSE-infected cattle.
- Make BSE a "notifiable" disease and implement a policy that all confirmed positive animals are condemned and incinerated.

The UK on July 12, 1988, implemented a condemn-and-incinerate policy and on July 18, 1988, implemented a ruminant feed regulation prohibiting the feeding of mammalian materials back to ruminant animals (BSE Inquiry 2000).

An important lesson learned from the BSE experience in the UK was that the practice of feeding ruminant derived MBM back to ruminants served to spread BSE (WHO 2002). Hence, banning this practice served as the primary defense mechanism in preventing transmission of the disease among the animal population, as reflected in Figure 3, which shows that the number of confirmed cases in the BSE epidemic peaked in 1992 and steadily declined thereafter. The peak of the epidemic in the UK correlated with the typical length of the disease's incubation period (3 to 5 y) and thereby supported a direct link to contaminated material's being present in cattle feed and the necessity of the feed ban regulation (Denny and Hueston 1997; Brown and others 2001). Representing the epidemic data by year of birth (Figure 4) makes the importance of the restrictions on feed ingredients even more obvious and further confirms the proposed incubation period. Note that putting the MBM ban to ruminants in place in July 1988 resulted in an immediate drop in the number of new cases. Removal of the specified risk materials (called specified bovine offals or SBO by the British) further lowered the number of new cases. Ironically, the number of new cases had fallen to very low levels even before the actions taken in 1996 to remove rendered mammalian proteins from all animal feeds (DEFRA 2005, OIE 2005).

Table 3—Relative distribution of infectivity in a typical clinical case of BSE.

Tissue	Proportion of total infectivity (%)
Brain	64.1[a]/60.2[b]
Spinal cord	25.6[a]/24.1[b]
Dorsal root ganglia	3.8[a]/3.6[b]
Distal ileum	3.3[a]/9.6[b]
Trigeminal ganglia	2.6[a]/2.4[b]
Retina	0.04[a]
Tonsils	0.0[b]

[a]From EU (2001).
[b]From Comer (2003).

Removal of tissues (specified risk materials, SRMs) that accumulate the BSE infectious agent (that is, prions) also protects against BSE transmission risk posed by cattle that have been exposed but aren't showing clinical symptoms of the disease (WHO 2002) and serves as the single most important food safety risk mitigation intervention that helps to protect public health. For example, bovine distal ileum was shown to exhibit prion infectivity as early as six months post-experiment oral challenge (Wells 1994), while tonsils were shown to exhibit a small amount of prion infectivity at ten months post challenge (Wells 1998). If exposed animals were slaughtered without removal of such tissues, infective material could then potentially be passed into the animal or human food chains. Therefore, enforcement of these SRM removal regulations in both animal feeds and human food not only reduces BSE transmission risk to cattle but also reduces the food safety threat to humans who consume beef.

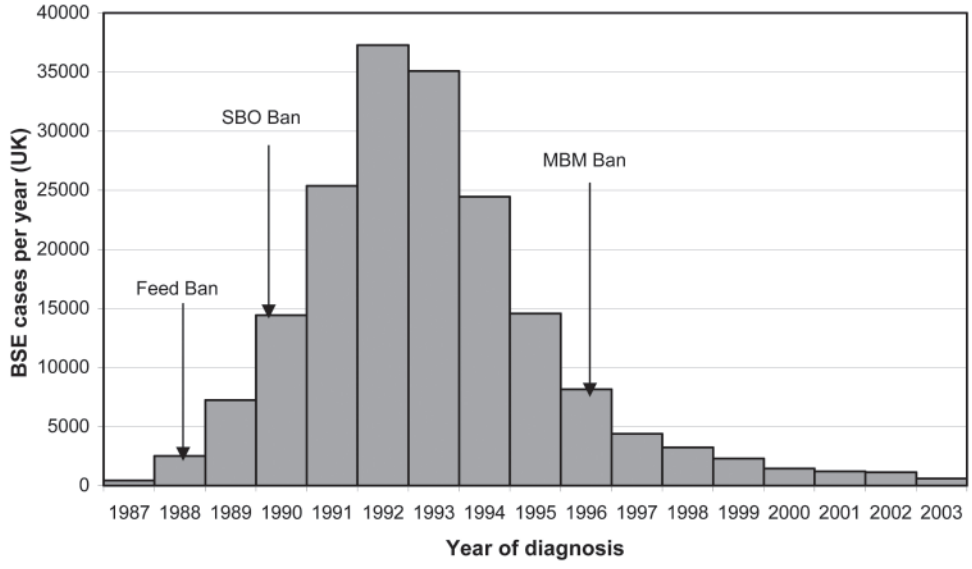

Figure 3—Nr of new cases of BSE in the UK since it was identified there in 1987. Data from OIE (2005).

Lessons from the European experience with BSE have had a significant impact on the handling of BSE prevention around the world. The main remedial interventions—against (a) transmission of the disease in the cattle population and (b) the risk that prion-contaminated tissues could enter the human food chain—that were imple-

Table 4—Chronology of actions taken to protect animal and human health from BSE[a].

Actions taken	UK	EU	CA	USA
Restricted ruminant protein from ruminant feed	1988			
Banned export of UK cattle born before July 1988 feed ban		1989		
Banned SBOs from human food	1989			
Banned importation of live ruminants (and products) from UK			1990	1989
Banned SBOs from animal food and export of SBOs to EU	1990			
Initiated active surveillance				1990
Banned export from UK of SBOs to non-EU	1991			
Restricted mammalian MBM from ruminant feed		1994		
Restricted mammalian protein from ruminant feed	1994			
MRM of bovine vertebral column (and export of it) banned	1995			
UK cattle and products (excluding milk) banned from export		1996		
Condemned all cattle over 30 mo from any use (except hide leather)	1996			
Restricted MBM from all animal feed/fertilizer	1996			
Restricted most mammalian protein from ruminant feed			1997	1997
Prohibits import of live ruminants and most products from all Europe				1997
Destroyed all offspring of BSE cattle born on or after August 1, 1996	1999			
Banned sheep and cattle SRM in EU		2000		
Prohibited all rendered animal protein product imports		2000		
Prohibited all rendered animal protein product imports, unless BSE-free			2000	
Banned MRM from cattle, sheep and goats	2001			
Restricted mammalian protein from all livestock feed		2001		
Began immunologic brain exam of all slaughtered cattle >30 mo	2001			
Began routine testing of AMR product for spinal cord tissue				2002
Banned downer cattle and SRMs (>30 mo) from human food supply			2004	2004
Initiated "test and hold" policy				2004
Banned MSM from human food				2004
Initiated expanded surveillance program			2004	2004
Banned SRMs and MSM from human food, cosmetics, and dietary supplements				2004

[a]SBO = specified bovine offal, MBM = meat and bone meal, SRM = specified risk material, MRM = mechanically recovered meat, AMR = advanced meat recovery, MSM = mechanically separated meat.

mented by governments in Europe and North America are outlined in Table 4.

A recent report by the European Association for Animal Production (EAAP 2003) suggested that the UK epidemic has neared an end and will not recur. It also concluded that the EU is left with three main BSE issues: (1) the remaining uncertainty as to BSE's origins, (2) the uncertain future of vCJD, and (3) what should be done with the 16 million tons of animal byproducts that are produced each year.

The Canadian Experience

A preliminary positive BSE diagnosis in Northern Alberta, Canada, was reported on May 16, 2003. This case was confirmed positive by the Canadian Food Inspection Agency's National Center for Foreign Animal Disease on May 18, 2003, and the UK's international reference laboratory on May 20, 2003. The cow actually was slaughtered on January 31, 2003, and was, at the time, unable to walk (that is, a non-ambulatory, recumbent "downer"). As a result of a postmortem pneumonia diagnosis, the carcass was condemned and did not enter the human food supply, although it was rendered and likely ended up in non-ruminant animal feed (CFIA 2003). A sample of brain tissue was collected as part of the Canadian BSE surveillance program, but processing of the sample at the laboratory was delayed, ironically, as a result of the high numbers of CWD surveillance samples being examined.

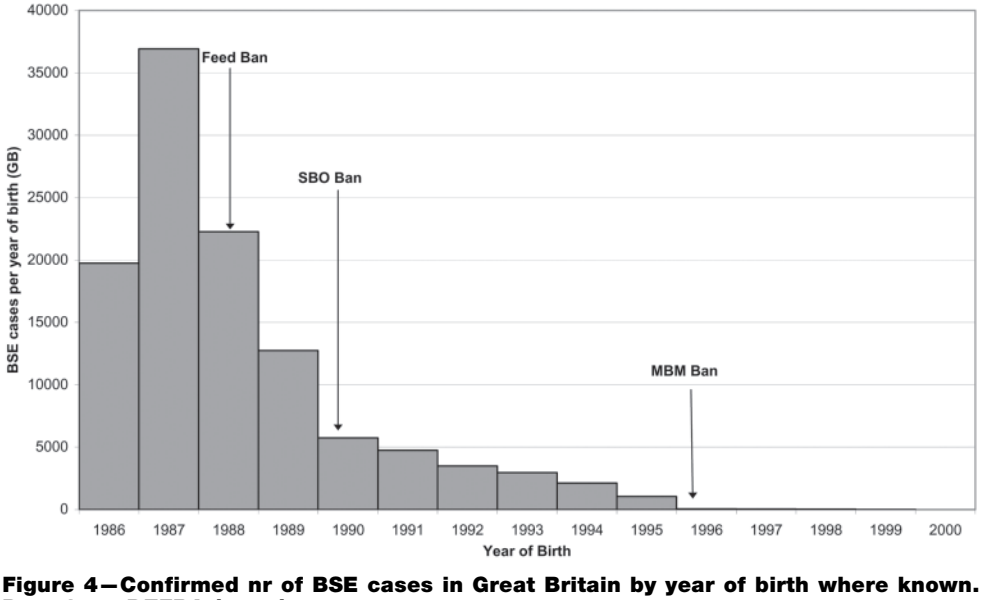

Figure 4—Confirmed nr of BSE cases in Great Britain by year of birth where known. Data from DEFRA (2005).

- An epidemiological investigation by CFIA revealed the following:
- The animal was born in Canada (95% confidence).
- The animal was between 6 and 8 y old.
- The 6 mo prior to the ani-

mal's death were spent as part of an 80-cow herd established in 2001–02 from 2 lines of cattle.

A total of 2700 cattle were destroyed as a result of the investigation, and the 2000 head of older cattle (>24 mo of age) were tested, with no additional cases of BSE detected (CFIA 2003). The age of the cow and information attained during the CFIA trace of this cow was consistent with the theory that it was infected through consumption of contaminated MBM sometime close to the August 1997 ban of this feeding practice. CFIA was unable to determine if the MBM was of Canadian or U.S. origin (approximately 50% of MBM consumed in this region was imported from the U.S.). The rendered remains of the infected cow were traced forward to pet food and animal feed. Up to 1800 farms may have received infective materials. The CFIA inspections revealed excellent records of compliance with feed regulations, suggesting that the risk to ruminants was minimized. CFIA went on to conduct 170 on-farm investigations and found that 99% encountered no exposure, further verifying very low risk to the cattle or human populations due to this one BSE positive cow (CFIA 2003).

The CFIA took the following quick actions (CFIA 2003):

- Required the removal of SRM from carcasses and prohibited the export and use of SRM in food for human consumption. SRM was defined as the skull, brain, trigeminal ganglia (nerves attached to the brain), eyes, spinal cord, and dorsal root ganglia (nerves attached to the spinal cord) of cattle aged 30 mo or older (scientific research has shown that these tissues in cattle younger than 30 mo rarely contain the infective agent); and the tonsils and distal ileum (portion of the small intestine) of cattle of all ages;
- Prohibited the sale or import for sale of food products containing SRM under the Food and Drug Regulations from countries that are not BSE-free.

These actions were followed by improvements to the tracking and surveillance systems in January 2004 (CFIA 2004), including the following:

- Enhanced enforcement activities associated with the existing cattle identification system.
- An increase in BSE testing levels, with a target of at least 8000 animals tested in the first year (2004), rising to testing levels of 30000 or more animals per year in following years (Canada actually tested nearly 24000 cattle in 2004, with a total slaughter cattle population of approximately 3.25 million).
- Accelerated development over the next 2 y of a more comprehensive cattle identification program that uses new technologies and integrates approaches with trading partners and existing programs.

Upon release of the BSE finding in May 2003, the U.S., Mexico, and many other countries around the world imposed a ban on the import of Canadian beef. Cattle prices dropped from $107 CND per hundredweight to around $30 CND within an 8-wk period. The trade embargo resulted in huge financial losses for Canada because Canada exports 50% of its beef, with 70 to 80% of exports destined for the U.S. (Francl 2003). As a result of the trade ban, U.S. imports of Canadian beef dropped from a high of about 1.1 billion lb in 2002 to 700 million lb in 2003 due to the trade ban implemented after the BSE case in May of that year. APHIS examined Canada's risk-mitigation strategies (for example, removal of SRMs and dedication of facilities) and categorized select beef, veal, sheep, and goat products as "low risk." In turn, trade restrictions were eased 4in August 2003 to allow import of trim and boneless beef cuts that originate from cattle less than 30 mo of age (ERS 2004). Further import permits have followed, including those for ground beef, hot dogs, and various other processed meats, and the trade situation continues to evolve (APHIS 2004b).

The 2nd and 3rd BSE-positive cattle in Canada were confirmed on January 2 and January 11, 2005, respectively. The first of these 2 cases was identified in an animal that was born in 1996, before Canada's implementation of mammalian-to-ruminant feed ban regulations. However, the 2nd case was born within the year after the implementation of the feed regulations. Both cases were investigated by Canadian officials (CFIA 2005a, b). Because of the younger age of the 2nd animal, the U.S. also sent a technical team to Canada to investigate the circumstances of this case. The findings of that investigation were to be used in consideration of the most recent regulatory position of the U.S. with regard to Canadian beef imports (USDA 2005). All countries dealing with BSE have observed cases born shortly after the implementation of MBM feeding bans, indicating the existence of an adoption period during which the new regulations achieve high levels of compliance. This last Canadian case should be considered in light of such international experience.

The U.S. Experience

USDA announced on December 23, 2003 that a cow slaughtered on December 9, 2003, at a facility in Moses Lake, Wash., had tested positive for BSE. APHIS and USDA's Food Safety and Inspection Service (FSIS) quickly mobilized to investigate this problem and protect animal and public health. The most recent herd from which the cow originated in Mabton, Wash., was put under quarantine. The following day, FSIS began a Class II meat recall of 10410 lb of beef generated from 20 independent cows slaughtered along with the BSE-positive cow (APHIS 2004c).

Immediately following the announcement of the BSE case in the U.S., countries around the world quickly took action to ban beef imports from the U.S. For 2 trading days following the announcement, live cattle futures prices dropped the maximum allowable (1.5¢/lb for a single trading day) and live cattle cash prices dropped to $75/cwt. In the months leading up to December 23, live cattle prices were $90 to 100/cwt (Petry 2004). By September 2004, the market had recovered fairly well, with prices averaging around $84/cwt (AMS 2004). The U.S. market has fared much better than neighboring Canada, which can be attributed to a lesser dependence on exports (10% of the U.S. market) (ERS 2004).

APHIS announced on December 27, 2003, that the cow in question originated in Alberta, Canada, and was imported into the U.S. in August 2001. The age of the cow was 6½ y. Based on this information, it was theorized and later confirmed that this cow was born before the mammalian-to-ruminant feed ban regulations of 1997 were implemented and thereby was likely infected via consumption of contaminated MBM (APHIS 2004c).

Secretary of Agriculture Ann M. Veneman announced on December 30, 2003, the following actions:

- A ban on non-ambulatory disabled ("downer") cattle from the human food chain.
- A "test-and-hold" policy that mandates that meat from cattle that are tested for BSE must be held until test results are obtained.
- Removal of SRMs from the human food supply.
- Strengthening of advanced meat recovery (AMR) rules by banning spinal cord and dorsal root ganglia.
- A ban on the use of mechanically separated beef from the human food chain.
- A ban on air-injection stunning.

These rules were issued as interim final rules (except the test-and-hold policy, which was issued as a notice) on January 12, 2004 (APHIS 2004c).

Also on December 30, 2003, the Secretary of Agriculture announced formation of an International Subcommittee of BSE ex-

Table 5—Comparison of surveillance programs for TSE diseases.

TSE	Country/region	Total nr tested[a]	Test protocol	Total nr of cases confirmed[a]
BSE	Japan	1.2 million (2004)	All slaughtered cattle tested since 2001. Fallen stock included in 2004.	16[b]
	EU (excluding UK)	>10 million (2003)	All slaughtered cattle aged over 30 mo and all fallen stock aged over 24 mo	>8000[b]
	UK	>460000 (2003)	All human-consumption cattle aged over 30 mo and all fallen stock aged over 24 mo	>180000[c]
	USA	>375000 (since June 1, 2004)	Revised plan: test as many as possible from high-risk population in 12- to 18-mo period	2[d]
	Canada	> 47000[e]	Testing from at-risk population	4[b]
CWD	USA[d]	31 elk herds, 8 deer herds	States survey for farmed cervids with APHIS support since 1997	Depopulated
		250000+[f]	State wildlife agencies with APHIS funding for free-range testing in 2002–03	592[f]
	Canada	17466[g] (2003)	CFIA tests for TB in each herd every 3 y and at that time inspects the animals for signs of CWD	3 herds
		13289	Saskatchewan Cervid CWD Surveillance & Certification Program, 1997–Jan. 2004	40 herds; 21 wild deer (2003)
Scrapie	EU[b]	551441	Active monitoring—rapid/confirmatory in 2003	1833
	UK		—	>3100 (since 1993)
	USA[d]	12508	SOSS[h]: Scrapie Ovine Slaughter Surveillance (4/1/02–3/31/03)	0.2%
	Canada[i]	675 (2003)	Reportable to CFIA—those known to be infected or exposed are destroyed	27
CJD/vCJD	UK[j]	160 (2003)	Surveillance unit in Edinburgh—based on referrals, that is, clinical, death certificates, and other sources	147
	USA[k]	284 referrals (2003)	Natl Prion Disease Pathology Surveillance Center at Case Western reports results to CDC	191 CJD, 0 vCJD
	Canada[e]	30	CJD SS (Surveillance System)—cases reported as suspected	1

[a]Represents approximate cumulative total unless otherwise noted.
[b]From OIE (2005).
[c]From DEFRA (2005).
[d]Dec. 2003 case imported from Canada (APHIS 2004c).
[e]From Canadian Food Inspection Agency Web site, www.inspection.gc.ca/
[f]From Progress Report on the Plan for Assisting States, Federal Agencies and Tribes in Managing Chronic Wasting Disease in Wild and Captive Cervids (October 2002 to September 2003), www.cwd-info.org/pdf/CWD_Progress_Reports.pdf.
[g]From Brian Peart, DVM, CFIA, personal communication, Aug. 25, 2004.
[h]From APHIS (2004f).
[i]From Penny Greenwood, DVM, CFIA, personal communication, August 25, 2004
[j]From Food Standards Agency (UK) Web site, www.food.gov.uk.
[k]From National Prion Disease Pathology Surveillance Center, www.cjdsurveillance.com/.

perts to conduct a review of the USDA response. Team members included Prof. U. Kihm and Dr. D. Heim of Switzerland, Prof. W. Hueston of the U.S., Dr. D. Matthews of the UK, and Prof. S.C. MacDiarmid of New Zealand. The committee met for three days in January and released a report on February 4, 2004. One recommendation of the team was to greatly expand the surveillance program to include cattle over 30 mo of age from the high-risk population (defined below), as well as to include a subset from the over 30-mo-and-healthy group (Kihm and others 2004).

In 2004, regulators pushed forward to ensure the safety of beef in America, with APHIS initiating a greatly expanded surveillance plan and FDA publishing enhanced efforts to keep BSE out of the human food chain.

The expanded surveillance plan was announced by APHIS on March 15, 2004 (APHIS 2004d). A comparison of this and other surveillance programs is provided in Table 5. It was described as a one-time effort to obtain a "snapshot" of the BSE situation in the U.S. and was initiated on June 1, 2004 with the goal of testing as many cattle from the target high-risk population as possible within a 12- to 18-mo period. During the period of expanded surveillance, from June 1, 2004 to June 2005, APHIS has sampled over 375000 cattle from the high-risk population. High-risk animals include cattle over 30 mo of age that fall into the following categories:

- Non-ambulatory cattle.
- Cattle with signs of central nervous system disorder.
- Cattle exhibiting other signs of BSE, such as wasting or injury.
- Dead cattle.

According to APHIS calculations, sampling 201000 animals would allow detection of BSE at the rate of 1 positive animal in 10 million adult cattle with 95% confidence, assuming that all of the positives were in the targeted high-risk population. If 268500 animals were sampled, the confidence level would rise to 99% (approximately 32 million cattle were slaughtered in the U.S. in 2004) (APHIS 2004d). The Institute of Food Technologists (IFT) issued a comment to USDA, encouraging full implementation of the expanded plan, suggesting that APHIS include economic incentives to ensure producer compliance, and calling for increased funding of BSE research.

Since June 1, 2004 three animals have given mixed or 'inconclusive' test results (2 in June and 1 in November, 2004), meaning that the sample came back positive for BSE by the rapid-screening assay. After further testing (IHC) all 3 were found to be negative for BSE. Recently, at the reguest of the Inspector General (who is directing a review of BSE-related activities), these inconclusive samples were retested using a second confirmatory method (SAF-immunoblot) with 1 yielding a BSE-positive result. This sample was then sent for further testing and on June 24, 2005 it was confirmed positive for BSE. As a

result, USDA has revised its protocol to include dual testing (IHC and SAF-immunoblot) of all future 'inconclusive' test results. It is important to note that the animal in question was a 'downer' and, therefore; due to the safeguards put in place by USDA and FDA following the December 2003 case of U.S. BSE, it did not enter the human food chain nor the ruminant-to-ruminant feed supply.

An interim final rule published by FDA and FSIS on July 14, 2004 (FDA 2004a) announced the ban of SRM, small intestine of all cattle, material from non-ambulatory disabled cattle, material from cattle not inspected and passed for human consumption, and mechanically separated beef, from human food, including dietary supplements and cosmetics. This ban did not include tallow (containing no more than 0.15% hexane-insoluble impurities) and tallow derivatives. FDA also published an advanced notice of proposed rulemaking that would require companies producing human food and cosmetics that are manufactured with, processed with, or otherwise contain material from cattle to keep records to prove that they did not use prohibited cattle materials (FDA 2004b).

Following an extensive risk assessment, USDA on December 29, 2004, created a "minimal risk region" status as a designation that establishes conditions under which a country may be allowed to export live cattle under 30 mo of age (and certain other commodities) to the U.S. Canada was the first and only country initially placed on that list. This regulatory action was published on January 4, 2005, and was to take effect on March 7, 2005 (APHIS 2005). Even though APHIS undertook a thorough investigation of the science to support this action (APHIS 2004e), it has met substantial resistance. The first was a preliminary injunction filed by the Ranchers Cattlemen Action Legal Fund (R-CALF) to the U.S. District Court of Montana (Edwards and others 2005). The second was delivered in the form of a vote by the U.S. Senate to disapprove the regulation. As a result of this resistance, the effective date for this regulation has been suspended indefinitely.

Public Reaction to BSE

Data from both Canada and the U.S. indicate that public confidence in the safety of the beef supply did not waiver significantly as a result of the revelation of BSE-positive cattle in North America.

Data from CanFax, a Canadian market analysis organization, suggested that, despite discovery of a case of BSE in Canada in May 2003, per-capita meat consumption within Canada increased slightly from 49.0 lb in 2002 to 51.5 lb in 2003 (CanFax 2004).

The National Cattlemen's Beef Association's beef demand index in the U.S. increased 10.4% from first-quarter 2003 to first-quarter 2004 (NCBA 2004). This index accounts for per-capita consumption and consumer spending on beef . The Cattlemen's Beef Board of NCBA sponsored a consumer survey that measured consumer confidence at 90% in January 2004 (CBB 2004). These strong indicators suggest that consumer confidence in the safety of the American beef supply remains high.

The Japanese Response

The first confirmed case of BSE in Japan was diagnosed in September 2001. Subsequently, the country instituted a mandatory ban on the use of ruminant MBM as animal feed in October 2001 (Japan-U.S. BSE Working Group 2004). Japanese per capita beef consumption dropped 42% in the month following the announcement of the first indigenous Japanese case (Japan 2003), demonstrating the disparity in consumer confidence compared to the U.S.

Japan began testing all slaughter cattle for BSE on October 18, 2001; however, it did not implement testing of cattle from the aforementioned "high-risk" group until April 2004, marking a significant difference in the American and Japanese approaches to surveillance. Japan has tested more than 3 million cattle and had 16 cases (OIE 2005), 2 of which were only 21 and 23 mo old (ProMed-mail 2003). Positive diagnoses of cattle younger than 30 mo have occurred rarely and are generally thought to be due to exposure to an unusually large dose of infective prions (FSIS 2004). However, one of these cases has been labeled "atypical," and both remain questionable because they tested negative for BSE using the "gold-standard" immunohistochemistry (IHC) test (ProMed-mail 2003; Japan-U.S. BSE Working Group 2004).

Japan was the largest importer of American beef, accounting for nearly $1.2 billion of total beef exports of nearly $3.3 billion in 2003 (ERS 2004). Accordingly, the biggest blow to the American cattle industry after the December 2003 BSE case in Washington State came when Japan closed its doors to those imports. Talks between APHIS and Japanese Food Safety Commission officials ensued, and a final report was issued on July 22, 2004 (Japan-U.S. BSE Working Group 2004). The Japanese initially insisted that the U.S. test all cattle to reestablish trade, but the U.S. argued that testing cattle less than 30 months has no scientific basis because BSE cannot be reliably detected early in the incubation period. Discussions may result in a change to Japanese policy that could open the door to U.S. imports because 80% of U.S. slaughter cattle are 20 mo of age or younger (ERS 2004; Japan-U.S. BSE Working Group 2004).

A joint press statement was released by the governments of Japan and the U.S. on October 23, 2004, stating that two-way trade could resume upon completion of regulatory processes currently underway in both countries (modification of testing procedures in Japan and implementation of import procedures by the U.S.) and development of a marketing program specifically for Japan (USDA 2004). This program, the Beef Export Verification Program, will result in certification by USDA's Agricultural Marketing Service that U.S. beef and beef product exports meet requirements as presented in the agreement. The Honorable Mike Johanns was sworn in as the 28th Secretary of Agriculture on January 21, 2005, and openly acknowledged that restoration of beef trade with Japan was the first priority on his agenda.

Human TSEs

The human variety of TSE exists in several different forms, including Kuru (transmitted via ritualistic cannibalism); GSS disease (genetic mutation); classic Creutzfeldt-Jakob disease (CJD); and variant CJD (vCJD).

Classic CJD has three forms: (1) sporadic, (2) familial, and (3) acquired (through transplantation of infected tissues or use of contaminated surgical equipment for a medical procedure—also referred to as iatrogenic). Sporadic CJD is also known as somatic or spontaneous CJD because it is thought to arise through either somatic mutation or spontaneous conversion. It occurs in 1 in 1 million people, accounts for 90% of all CJD cases, and is not known to be contagious. Familial or hereditary CJD is associated with a genetic mutation and accounts for 5 to 10% of cases, while iatrogenic is unintentional, accounting for less than 5% of all cases (Prusiner 1998; WHO 2002).

vCJD was first diagnosed in 1995 in the UK. From May to October of that year, 3 people who were much younger than most classic CJD victims (ages 16, 19, and 29 y) displayed unusual neuropathology. Autopsy demonstrated unusual accumulation of PrP, called amyloid plaques—an abnormality that occurs in only 5 to 10% of classic CJD cases. Also, psychiatric symptoms were more common to the initial presenting signs that occur with classic CJD. They displayed prominent ataxia, absence of periodic electroencephalographic activity, and a comparatively prolonged illness (Brown and others 2001; WHO 2002). Epidemiological data strongly suggest that vCJD was transmitted to humans via consumption of BSE-contaminated meat prod-

ucts. Such contamination may have resulted from infected tissues (SRM) being mixed with muscle meat through mechanical deboning systems. Importantly, muscle tissue itself has not been shown to carry infectivity (Brown 2001, 2003). As of February 2005, there have been 155 probable confirmed cases, resulting in 150 deaths due to vCJD in the UK (CJD Surveillance Unit 2005), 7 cases in France (ProMed-mail 2004), and 1 case each in Canada, Ireland, Italy, the U.S., Japan, and, most recently, the Netherlands. A caveat to the Canadian, Irish, and U.S. (and likely the Japanese) cases is that all were diagnosed in people who had resided in the UK and were likely infected during that time (CDC 2004).

Susceptibility to vCJD is characterized by a polymorphism at codon 129 of the human genome, which codes for valine or methionine. Homozygosity for valine appears to decrease the risk of infection as homozygosity for methionine is common to all clinical cases of vCJD genotyped (Ironside and others 2002). Infectivity of vCJD has been found once in tissues of an MV heterozygote vCJD transfusion recipient who died of unrelated causes (Llewelyn and others 2004).

Live Animal Testing

Live-cattle testing would be extremely beneficial to the BSE surveillance system. Current methods are performed post-mortem and are targeted at high-risk animals. A live test would presumably allow earlier detection of the disease, which would advance our understanding of the epidemiology of BSE infection and enhance the possibility of eradication of this disease.

USDA has been critical of current testing procedures because they may not detect infected animals early in the incubation period, thereby allowing the possibility of false negatives (FSIS 2004); development of enhanced diagnostics would reduce such possibilities. One example of a seemingly applicable analysis technique is the use of sodium phosphotungstic acid to preferentially precipitate prions. Use of this method has been shown to increase Western blot sensitivity by up to 3 orders of magnitude (Wadsworth and others 2001; Glatzel and others 2003). Further study of the practical application of this technique as a means of enabling detection earlier in the disease cycle may provide a means for elimination of animals that appear healthy even though they are infected with BSE prions.

Development of such diagnostics, as suggested by the Secretary's Subcommittee on the U.S.' Response to the Detection of a Case of Bovine Spongiform Encephalopathy (Kihm and others 2004) could go a long way toward characterizing the amount of BSE infectivity present in the U.S. cattle population.

Adaptive Risk Management in the Face of Evolving Science

Prions present one of today's great scientific enigmas and one that has a particularly significant effect on the food industry, regulators who work to keep our food supply safe, and the public who expect animal products that they consume to be safe. A number of TSEs have been discovered, each with differing symptoms, genetics, transmissibility, and pathology. Expression of TSE in a species is affected by the magnitude of exposure dose to PrP^{res}, the hosts PrP genome, the route of exposure, and the age at exposure.

New TSE research appears in the scientific literature or popular press almost weekly. TSEs are an active research area, with multiple in-vivo and in-vitro approaches, using a wide array of both wild-type and transgenic experiment animals. Given that the expression of TSE is very dependent on the specific infectious agent/host interaction, researchers must be very cautious when extrapolating results of experimental studies; for example, scrapie in mice and CWD in deer are not necessarily always equivalent to BSE in cattle.

Since the first official case of "mad cow" disease was diagnosed in the late 1980s, animal and public health officials have struggled to define, detect, prevent, quantify, and control this disease. Recognition that an animal health and food safety issue can have catastrophic global impact while resulting in very limited human illness and death has provided a hurdle to effective risk assessment, management, and communication. Meanwhile, governments have had to act on the basis of a rapidly evolving scientific understanding derived from epidemiological studies and laboratory research.

Today, the U.S., Canada, and many other countries have mandated removal of SRM from the food supply and restricted production practices that may lead to cross-contamination. They eliminated use of recycled mammalian materials from ruminant feed 6 y prior to the first appearance of BSE in indigenous North American cattle and have put into place extensive surveillance programs. To date, these measures appear to have successfully protected public health and upheld consumer confidence in the regulatory system. Nevertheless, science continues to evolve, and international trade remains significantly disrupted.

As pointed out in this report, developments in effective risk management and testing methods are important to the ultimate fate of this disease. Such methods would accelerate our ability to identify asymptomatic animals and eliminate infectious materials, without adding to existing waste and environmental concerns. As researchers continue to investigate the science of TSEs, there is a need for increased funding and coordination of research and risk management efforts.

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