



**Assessment of Bovine Spongiform Encephalopathy
(BSE) risks associated with the importation of
certain commodities from BSE minimal risk
regions (Canada)**

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Executive Summary

On January 4, 2005, the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) published in the *Federal Register* a final rule (70 FR, Docket No. 03-080-3, pages 459-553) to amend the regulations regarding the importation of animals and animal products to 1) establish a category of regions that present a minimal risk of introducing bovine spongiform encephalopathy (BSE) into the United States (BSE minimal risk regions) via live ruminants and ruminant products and byproducts, and 2) add Canada to that category. That rule also established conditions for the importation of certain live ruminants and ruminant products and byproducts from such regions.

We are now proposing to amend the regulations to allow the importation of certain additional commodities from BSE minimal risk regions – currently, only Canada. This risk assessment evaluates the potential BSE risk associated with the proposed regulations. The risk assessment indicates that the proposed actions will continue to protect against the introduction and establishment of BSE into the United States.

Commodities discussed in this risk analysis reflect those that, in accordance with the World Organization for Animal Health (OIE) guidelines, can be safely traded under certain conditions. APHIS is considering allowing the importation of 1) live bovines (cattle and bison) that were born after the date when a ruminant-to-ruminant feed ban was effectively enforced; 2) blood and blood products collected under certain conditions; and 3) bovine small intestine, other than distal ileum, under certain conditions.

This risk assessment includes both quantitative and qualitative evaluations of the animal health risks associated with these products and the likelihood that these products imported from minimal risk regions (Canada) would introduce BSE infectivity into the United States and expose the U.S. cattle population. The analysis uses the approach recommended by the OIE (*Terrestrial Animal Health Code* Section 1.3 Risk Analysis) for trade-related animal health risk assessments, which focuses on determining likelihood of release (i.e., introduction of the disease agent), likelihood of exposing susceptible animals given release, and the magnitude of consequences given release and exposure.

The analysis includes consideration of the effects of proposed mitigations for each of these commodities as follows:

1. Live cattle and bison: live bovines were born on or after March 1, 1999.
2. Blood and blood products:
 - For all blood:
 - a. the blood is collected in a closed system.
 - For blood collected at slaughter:
 - b. the slaughtered animal passed ante-mortem inspection and
 - c. was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or a pithing process.

For fetal bovine serum:

- d. the dam passed ante-mortem inspection and was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or a pithing process.
- e. the uterus is removed from the dam's abdominal cavity intact and taken to a separate area away from the kill floor.

For blood collected from live donors:

- f. the donor must be free of clinical signs of disease.
3. Bovine small intestine: small intestine must exclude the distal ileum by removing at least 80 inches of the uncoiled and trimmed small intestine as measured from the cecocolic junction and progressing proximally toward the jejunum.

The analysis uses both qualitative and quantitative methods for various parts of the assessment. As part of the release assessment, we use quantitative methods to estimate the current prevalence of BSE in the standing adult cattle population in Canada. We use qualitative methods to describe the most likely outcomes of the release assessment. In the exposure assessment, we again combine both qualitative and quantitative methods. In those instances where we either cannot numerically represent the expected outcome, or where the numbers would be so low as to prevent their use in further calculations, we qualitatively assess the possible exposure. To conduct a quantitative assessment of the possible exposure we make assumptions expected to overestimate the overall risk in order to provide sufficient numeric input for the model.

The BSurvE model with modifications is used to quantitatively estimate the prevalence of BSE in the standing adult cattle population of Canada. As this model cannot predict future changes in prevalence, we qualitatively evaluate the available evidence to anticipate how the prevalence may change. Based on evidence from the United Kingdom (UK) and Europe about the effects of a feed ban, as well as on the results of simulation models, we expect that the prevalence of BSE in Canada will decrease continuously over the next several years. A key assumption underlying this expectation is that an effectively implemented feed ban will be sufficient to eventually eradicate BSE in a country's cattle population. Although the BSE epidemic curve in Europe exhibits a long tail, the assumption of eventual eradication of the disease resulting from a feed ban is consistent with epidemiologic simulation modeling predictions.

Although this scenario is the most likely, because we cannot provide an accurate prediction for the rate at which we might expect the already low prevalence to decrease, we cannot numerically represent the expected annual release over the time period of the analysis. Therefore this scenario is described qualitatively.

We quantitatively evaluated other less likely scenarios expected to over-estimate the overall risk. For this assessment, we assume that the August 2006 prevalence, calculated using the Bayesian Birth Cohort (BBC) model, remains constant over the next 20 years. Even if the BBC model were to slightly underestimate the current prevalence of BSE in Canada (an alternative current prevalence estimate is provided for sensitivity analysis), we expect that assuming it to remain constant at this level over the next 20 years would

overstate prevalence during the time horizon of the analysis. This assumption of constant prevalence, combined with the estimates of projected cattle imports from Canada, provide the values for release of infected live animals in this less likely scenario. This numeric input is necessary for the quantitative model used to inform the exposure assessment.

The exposure assessment for live animals qualitatively indicates that, because the most likely expectation is that Canada's prevalence will decrease over time, and because of the barriers to BSE transmission in the United States, that the likelihood of BSE exposure and establishment in the U.S. cattle population as a consequence of infectivity introduced via imports from Canada is negligible. In our quantitative consideration of less likely scenarios, the exposure assessment evaluates the impact of the numbers of infected animals imported, assuming constant BSE prevalence in Canada, on the likelihood of U.S. cattle exposure to BSE. We base our evaluation on the Harvard Center for Risk Analysis BSE simulation by Cohen et al., updated to incorporate new evidence and domestic regulations, and the proposed changes considered here. In order to provide time for several potential infectivity cycles, this model tracks BSE release and exposure in the United States over 20 years. In the current analysis, it indicates that even with risk-inflating assumptions about the possible level of infectivity released into the United States, there is little spread of disease to U.S. animals. Assuming the less likely scenario of constant BSE prevalence in Canada, the model predicts that over the 20 years of the analysis, importation of approximately 19 infected animals leads to approximately two U.S. cases as secondary spread. Since most animals are slaughtered during the lengthy incubation period, only 0.67 of all 21 infected animals predicted by the model would live to show clinical signs.

Considering evidence provided in the consequence assessment, we expect that even the unlikely scenario evaluated in the quantitative release and exposure assessments results in negligible economic costs of BSE. Although human health is not the focus of this assessment, we note that the quantitative model, which includes multiple sources of risk over-estimation, indicates a negligible level of infectious agent that may be potentially available for human exposure. We conclude that the consequences and resulting risk of importation of live bovines under the conditions specified are negligible.

The risk of release and exposure via blood and blood products, and bovine small intestine other than distal ileum, were evaluated qualitatively. We conclude that the joint likelihood of BSE release and subsequent exposure of bovines to infectivity from either of these commodities is negligible. We further conclude that this negligible likelihood would result in extremely few or no U.S. cases of BSE. Therefore, the consequences and resulting risk of the importation of these commodities are negligible.

I. Introduction

The Bovine Spongiform Encephalopathy Minimal Risk Regions (BSE MRR) rule: The BSE MRR rule (APHIS 2005) established the criteria for a BSE minimal risk region, determined that Canada met those criteria, and specified the commodities permitted import under the regulation. We are not proposing to amend either the criteria for a BSE minimal risk region, or the designation of Canada as meeting those criteria in this rule. We are, however, proposing to amend the commodities permitted for import under the MRR designation.

The following summarizes those aspects of the rule that are relevant to the current proposal:

The criteria for minimal risk regions ensure that such regions have taken appropriate control measures to maintain a low prevalence of BSE and conduct surveillance in accordance with international guidelines to monitor the presence of disease. Existing regulations allow the importation, under certain conditions, of live ruminants and certain ruminant products and byproducts. Previous risk assessments concluded that live bovines could be safely imported as long as they were slaughtered before they were 30 months of age. To ensure slaughter by this age limit, regulations were established concerning identification, controlled movements, and monitoring. These assessments also concluded that bovine meat and meat products could also be imported under certain conditions.

Both the United States and Canada have conducted extensive surveillance programs since the middle of 2004. Since January 4, 2005, when the final rule recognizing Canada as a minimal risk region was published, seven cases of BSE have been identified in Canada. In the United States, two indigenous cases of BSE have been identified - one in July 2005 and one in March 2006. The additional information obtained from these surveillance efforts and additional epidemiological analysis of all of the BSE cases support the substantive analysis outlined in this document. This analysis supports the proposed changes to allow the import of certain additional live bovines, certain bovine blood and blood products, and bovine intestines, other than the distal ileum.

Scope

USDA APHIS' regulatory authority under the Animal Health Protection Act covers factors impacting the health of livestock. Therefore, the scope of this risk assessment is limited to animal (specifically, bovine livestock) health pathways and consequences. Other potential impacts on aspects of the "human environment,"¹ including public health, are addressed to comply with the National Environmental Protection Act (NEPA) in the accompanying environmental assessment (APHIS 2006).

¹Under NEPA regulations, "human environment" is interpreted to include the natural and physical environment and the relationship of people with that environment.

To facilitate the quantitative analysis of the likelihood of introduction and spread of BSE via imports of live bovines, we use a screening approach which includes all bovines that would be allowed entry under the proposed regulation. Thus, the analysis is not incremental in that we include animals that are already allowed entry under current regulations. We recognize that by including in the analysis animals that are already allowed entry (for slaughter by 30 months of age) we are increasing the estimated likelihood of introducing infected animals beyond that which may result from the proposed imports alone. If the risk associated with the entire group analyzed is acceptable then no further analysis is necessary. However, the analysis is not cumulative in that we do not consider the level of indigenous infectivity that may currently be present in the U.S. cattle population.

Format

The format of this risk assessment follows OIE guidelines. The risk assessment proper is preceded by a Hazard Identification section in which we specify for what pest or disease of livestock we are assessing the risk. In this case, we are restricting the assessment to BSE that may be introduced in live animals and certain bovine-derived products from Canada, a BSE minimal risk region. The risk assessment itself includes the four sections specified by the OIE's *Terrestrial Animal Health Code* Section 1.3 Risk Analysis (OIE 2006b). The Release Assessment evaluates the likelihood that animals or products proposed for import from Canada are infected with the BSE agent. The Exposure Assessment evaluates the likelihood of exposure, establishment and spread of the BSE agent in the United States given that it has been released. The Consequence Assessment addresses the impacts expected if, as a result of the proposed rule, BSE were to occur in the United States. Finally, in the Risk Estimation, we combine the findings of the release, exposure, and consequence assessments to express the overall risk of BSE in the proposed commodities from the minimal risk region (Canada).

This risk assessment, according to the approach as it is applied across a variety of disciplines, breaks down the possible pathways for the undesired outcome (in this case, the establishment of BSE in the U.S. cattle population) into a series of steps, or nodes. Some of the nodes are in series, in that in order for one to occur, a previous one must have occurred. The likelihood of occurrence of a series of sequential steps is the product of the likelihood of each of the individual steps occurring. This multiplicative effect takes place whether or not an analysis is performed quantitatively or qualitatively. Some steps in the risk pathways can occur without the occurrence of other steps. These are said to function in parallel, and are therefore, additive in their impact on the likelihood of the undesired outcome. Because the impact of any specific step depends on its relationship to other steps, its importance to the overall likelihood of the undesired outcome cannot be understood in isolation from the rest of the pathway. Therefore, in risk assessment, although we analyze the likelihood of each individual step in the process, we interpret its significance in the context of the entire process. For example, in this assessment, we present evidence for the likelihood of release of infected animals from Canada to the United States. However, the impact of the amount of infectivity introduced cannot be understood until it is interpreted together with the outcome of the Exposure and Consequence Assessments.

History of BSE in Canada

As of October 27, 2006, a total of nine BSE cases of Canadian origin had been confirmed. This number includes one case of Canadian origin that was identified in the United States in December 2003. The first native Canadian case was identified in May 2003, and was followed that year by the December case identified in the United States. In response to the finding of BSE in Canadian cattle, the Canadian Food Inspection Agency (CFIA) intensified their surveillance efforts and have identified seven additional cases through October 27, 2006.

Epidemiological investigations have shown that BSE initially entered Canada in the 1980s via an infected animal or animals that were imported from the UK. It is likely that rendered meat and bone meal (MBM) produced from these animals were included in cattle feed, a practice that was permitted at the time, and this practice led to the development of additional cases of BSE in Canadian-born cattle (USDA 2005a).

Canada imported 182 cattle from the UK between 1982 and 1990. Following the detection of an imported case of BSE in 1993, all remaining UK imports were slaughtered and incinerated, or returned to the country of origin (USDA 2005a). The BSE risk status of the Canadian birth cohorts was assessed based on demographic factors, age, and the BSE status of their UK herd of origin. The assessment indicated that of the 52 animals shipped to the Province of Alberta, three were from cohorts of UK cattle with BSE. One of these was the animal that tested positive for BSE in 1993; the resulting investigation determined that the other two had already died and most likely entered the feed processing system prior to the detection of the first case. Therefore, a likely scenario is that MBM containing specified risk materials (SRM) from one or more infected animals contaminated the Canadian feed system and was recycled during the early 1990s. Considering the average incubation period for BSE, CFIA believes that Canada's BSE cases represent the second generation (or amplification cycle) in that country (CFIA 2006).

Investigations conducted in 2003 and 2004, following the diagnosis of an indigenous case of BSE, revealed geographical proximity among the origins of all the Canadian BSE cases and the destinations of cattle imported from the UK (USDA 2005a). The destinations of the UK imports and origin of the Canadian BSE cases were clustered in a relatively small geographic area in central Alberta and western Saskatchewan. Further investigations carried out by CFIA revealed that renderers, feed mills and farmers across Canada are grouped by geographic and economic forces into "clusters" (CFIA 2006). Since the distribution of MBM in Canada is generally localized, the disease was most likely recycled primarily within a geographic feed zone unless infected cattle and/or contaminated MBM were moved to other areas. With one exception, epidemiological investigations completed by October 2006 indicate that all indigenous Canadian BSE cases were born and spent their first 12 months of life within the cluster area, or were exposed to feed from within the cluster area (CFIA 2006, CFIA 2006b). The exception

was an approximately 16 year old cow in Manitoba, which was determined to have a different phenotype than the other cases. The CFIA investigation reported that this case had a phenotype consistent with a less prevalent strain of BSE previously reported in Europe and the United States (CFIA 2006b). The detection of additional cases within either this recognized cluster or further clusters that might be defined in the future cannot be ruled out. Such detections do not necessarily negate the assumptions and findings of this assessment.

One of the regional rendering facilities in Alberta processing high risk BSE animals (downers and dead stock) used a particular low temperature “vacuum” process that does not reduce BSE infectivity (zero log reduction). This practice most likely allowed the recycling through the feed chain of infectious materials from high risk animals and further contamination of cattle feed prior to implementation of the feed ban. CFIA concluded that all indigenous Canadian cases detected to date have been associated with the cluster where this particular low temperature vacuum rendering system was used (USDA 2005a). After 1997, in compliance with the feed ban, prohibited ruminant material produced by the low temperature vacuum rendering system was not used in ruminant feed, although this ruminant derived material was still available for feeding to non-ruminants. To deter farmers and ranchers from accidentally or intentionally feeding prohibited material to ruminants, products containing ruminant derived material had to be labeled with the caution statement, “Do not feed to cattle, sheep, deer, or other ruminants.” Therefore, the implementation of the feed ban in 1997 reduced, if not eliminated, the recycling of BSE infectivity and greatly decreased the likelihood that cattle born after implementation of the feed ban would be exposed to the BSE agent.

II. Hazard Identification

This analysis focuses on the BSE risk that might be posed by the importation of live bovines born after the date of an effectively enforced feed ban, and the importation of certain commodities derived from cattle (blood and blood products and small intestines other than distal ileum) into the United States from Canada. The agent of interest in this analysis causes bovine spongiform encephalopathy (BSE).

BSE is not a contagious disease, and therefore is not spread through casual contact between animals. Instead, transmission requires that cattle ingest feed that has been contaminated with tissue from an infected animal. Several steps must take place for this to happen – an infected animal, carrying significant amounts of the infectious agent, must die or be slaughtered; tissues from that animal that contain the infectious agent must be sent to a rendering facility; the infectivity present in these tissues must survive inactivation in the rendering process; the resulting protein must be incorporated into feed and this feed must be fed to at least one bovine at a level adequate to result in infection given that animal’s age-specific susceptibility. As will be discussed later in this document, there are several barriers at different steps in this process that decrease the possibility of infection as outlined.

BSE is a progressive neurological disorder of cattle that research suggests is caused by a pathogenic form of a normally occurring protein known as a prion (PrP) (Bolton, et al. 1982; Prusiner 1994). BSE belongs to a family of diseases known as transmissible spongiform encephalopathies (TSEs). In addition to BSE, TSEs include, among others, scrapie in sheep and goats, chronic wasting disease in deer and elk, transmissible mink encephalopathy, and Creutzfeldt-Jakob disease (CJD) in humans.

The pathogenic form of the prion protein (PrP^{Sc}) is both less soluble and more resistant to degradation than the normal form (Taylor 2000; Taylor, et al. 1995). The PrP^{Sc} is extremely resistant to heat and to normal sterilization processes, making it difficult to inactivate with standard methods used to process human food and animal feed. Although rendering and other processes can partially inactivate PrP^{Sc}, the risk mitigation strategies (for meat and meat products) rely mainly on the elimination of tissues and organs known to carry infectivity.

The agent does not evoke a traditional immune response or inflammatory reaction (Khalili-Shirazi, et al. 2005), thus reliable ante-mortem diagnostic tests based on host reaction are not available. Definitive diagnosis requires post-mortem microscopic examination of brain tissue or detection of PrP^{Sc} in tissue samples.

The following paragraphs detail the relevant characteristics of BSE, including transmission, incubation period, tissue distribution, and infectivity of the BSE agent in cattle, its most common host.

II.A. *Transmission*

The primary source of BSE infection is commercial feed contaminated with the infectious agent. Scientific evidence (Wilesmith, et al. 1988; 1991; 1992) shows that feed contamination results from the incorporation of ingredients that contain ruminant protein derived from infected animals. Standard rendering processes do not completely inactivate the BSE agent. Therefore, rendered protein such as meat-and-bone meal (MBM) derived from infected animals may contain the infectious agent. Bans prohibiting incorporation of mammalian or ruminant protein into ruminant feed are imposed to mitigate the risk of BSE transmission.

Oral ingestion of feed contaminated with the abnormal BSE prion protein is the only documented route of field transmission of BSE (Prince, et al. 2003; Wilesmith, et al. 1988; 1991; 1992). However, results of a UK cohort study indicated that offspring of BSE-affected dams were at a higher risk of also developing clinical BSE, suggesting the possibility of maternal (vertical) transmission (Wilesmith, et al. 1997). These results are consistent with a rate of maternal risk enhancement of approximately 10 percent in the offspring born within 12 months of the dams' onset of clinical signs of BSE. Since the initial cohort study, modeling studies based on the epidemic data from the UK have indicated that the cumulative maternal risk is only 1 percent in calves born in the last 6 months of incubation of the disease in its dam (Donnelly, et al. 2002). More recent work on cases born after the 1996 feed ban fails to demonstrate evidence of maternal

transmission (Hill 2005). Thus, although maternal transmission may be possible, more recent epidemiologic evidence suggests that maternal transmission of BSE is unlikely to occur at any appreciable level, if at all.

Epidemiological studies and simulation modeling have indicated that most cases were likely exposed as calves (Wilesmith 1988) with most chances of becoming infected during the first year of life (Wilesmith, et al. 1992 and 1992a; Ferguson 1997; De Koeijer, et al. 2004). These findings suggest that susceptibility in cattle declines with age, and, therefore, young animals are most susceptible. One simulation study suggests that animals consuming BSE infectivity that are older than four months of age are less susceptible than younger animals. Specifically, this simulation estimates that susceptibility declines exponentially after the age of 4 months leveling off at 10 percent of the peak value (De Koeijer, et al. 2004).

Experience in the UK demonstrates that implementation of a ruminant-to-ruminant feed ban exerts downward pressure on the prevalence of BSE (Figure 1). Animal feed restrictions began in the UK in July 1988, when the use of ruminant MBM in ruminant animal feed was banned. In September 1990, the use of Specified Bovine Offals (SBO) was banned for use in any animal feed. This ban prohibited the use in any animal feed of bovine tissues with the highest potential concentration of infectivity. In 1994, the use of mammalian protein – not just ruminant protein – was banned from ruminant feed. In 1996, feeding of any farmed livestock, including fish and horses, with mammalian meat and bone meal (mammalian MBM) was completely banned. As a result of these bans to reduce the recycling of infectivity, the annual incidence of BSE fell by 99.4 percent from 36,680 in 1992 to 203 in 2005 (DEFRA 2006b).

When the UK epidemic is plotted by year of birth, the impact of the feed ban is striking. Although the data that are presented in the following figure and table represent the specific situation in the UK² during the years identified in the graph, we expect similar effects (i.e., downward pressure on the prevalence of BSE) in any country that implements a comparable feed ban.

² The data made available by DEFRA on its website are for Great Britain, which does not include Northern Ireland. These data also exclude the Channel Islands and Isle of Man. Records published elsewhere indicate that the vast majority of BSE cases in the UK have been detected in Great Britain (OIE 2006). therefore, epidemiologic patterns noted in Great Britain represent the overall UK experience.

Effect of the Feed Ban on BSE Cases in Great Britain

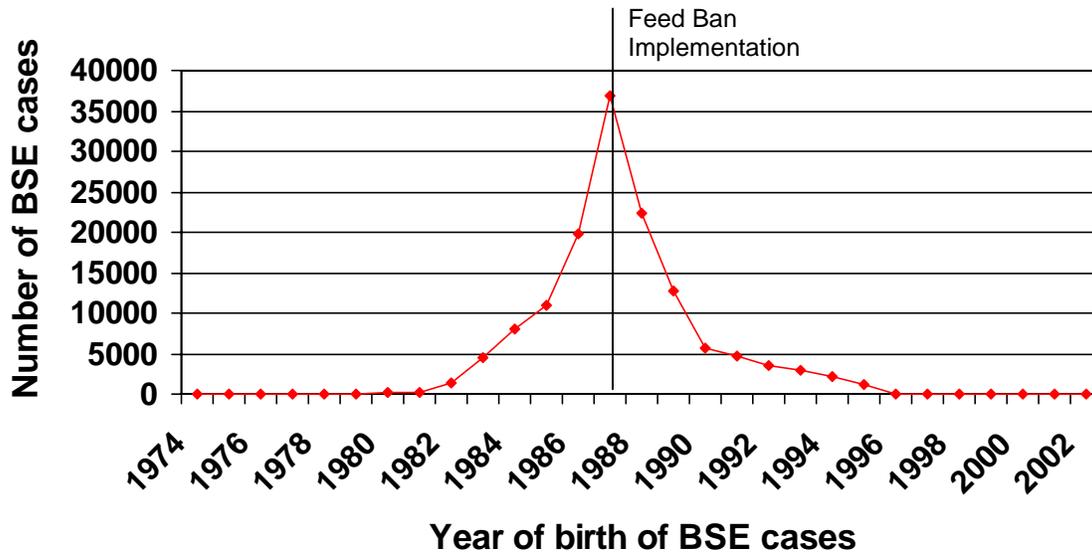


Figure 1. Confirmed cases in cattle born in Great Britain after feed ban implementation. **Note:** The first feed ban was implemented in the summer of 1988 (before fall calving). Source of data represented in figure and in Table 1: DEFRA 2006a.

The raw data that provided the basis for Figure 1 are reproduced in Table 1.

Table 1. Confirmed cases in Great Britain by year of birth, where known

Year	Cases	Year	Cases
1974	1	1989	12,748
1975	0	1990	5,747
1976	2	1991	4,779
1977	10	1992	3,531
1978	6	1993	2,997
1979	41	1994	2,179
1980	102	1995	1,099
1981	262	1996	67
1982	1,394	1997	45
1983	4,463	1998	37
1984	8,069	1999	23
1985	11,071	2000	5
1986	19,752	2001	5
1987	36,935	2002	1
1988	22,266	Unknown birth year	43,340
Total: 180,977			

Source: DEFRA 2006a.

Despite the dramatic evidence presented above, as of September 2006, 134 cases of BSE have been detected in UK animals born after the ban (BAB cases) reinforcement in 1996 (DEFRA 2006). Several analyses of the BAB cases suggest that the animals were likely to have been exposed to an exogenous feed source from continental Europe. For instance, based on the analysis of the first 16 cases (Wilesmith 2002) the author indicates that an exogenous (non-UK) feedborne source remains the most likely explanation, since trading of MBM was legally possible at ports of Continental Europe until the European-wide ban was introduced in January 2001. Significant amounts of ingredients for cattle feed were imported into the UK before 2001, and cross-contamination of feedstuffs and ingredients has occurred in a number of other BSE-affected countries. A recent report (Hill 2005) also indicates the association of BAB cases with imported feed until controls were strengthened throughout Europe.

II.B. *Incubation*

BSE has a long incubation period. Epidemiological data from the UK epidemic has demonstrated that, on average, cattle develop clinical signs four to six years after infection (Bradley 1991; Anderson, et al. 1996), though the incubation period can be longer or shorter than four to six years. In BSE, as in other TSEs, the total amount of infectivity in an animal increases throughout the incubation period reaching the highest load at the end, very close to the death of the animal. Infectivity is considered to increase exponentially after exposure, reaching 3 logs less than clinical cases by 70 percent of the incubation period, and 4.5 logs less than a clinical case at 50 percent of the incubation period (Comer and Huntley 2003).

The incubation period is thought to be inversely related to dose (e.g., low dose exposures have long incubation periods before clinical signs of disease become apparent). The Department for Environment Food and Rural Affairs (DEFRA) Veterinary Laboratories Agency (VLA) in the UK has carried out cattle oral challenge studies to determine the incubation period for a range of doses of BSE infected cattle brain (Anderson, et al. 1996). In the first attack rate experiments, groups of 10 calves were dosed orally with 3 X100g (100g on 3 successive days), 100g, 10g or 1g of brain tissue from clinically sick animals. All animals in the two higher dose categories (3x100 and 100gr, respectively), 7 out of 9 in the 10 g, and 7 out of 10 in the 1g trial groups developed clinical BSE. The incubation period (IP) for the 3X100g ranged between 33 and 42 months. The IP for the 100g was 33 to 61 months; for the 10g was 42 to 75 months; and for the 1g was 45 to 75 months. The remaining animals in this experiment were killed at 110 months after exposure and showed no pathological evidence of disease.

The second attack rate experiments extend these findings with lower doses. As of December 2005, at approximately 93 months post exposure, the authors have confirmed 3 of 5 animals as positive for BSE in the 1g trial group (IP 59-73 months), 6 out of 15 animals in the 0.1g group (IP 55-90 months), 1 out of 15 in the 0.01g group (IP 56 months), and 1 out of 15 in the 0.001g group (IP 68 months) (Matthews 2005 personal communication). The study is ongoing.

II.C. Tissue distribution and infectivity

Most of the information on the development and distribution of tissue infectivity in BSE infected cattle has been derived from experimental pathogenesis studies conducted in the UK (Wells, et al. 1994; 1998; 1999). In these studies, cattle were deliberately infected with BSE through oral exposure to the brain tissue of cattle with confirmed BSE. Subsets of the experimentally infected cattle were killed at regular intervals as the disease progressed. At each interval the tissues of the infected cattle were examined for histopathological changes consistent with BSE and for abnormal prion proteins. Also, at each interval, a mouse assay was done – i.e., tissues of the BSE infected cattle were injected intracerebrally and intraperitoneally into mice to identify those tissues of cattle containing infectivity.

The pathogenesis studies involved 30 animals, each of which received a single dose of 100g of infected brain at 4 months of age (Wells, et al. 1994; 1998; 1999). This dose is probably 10 -100 times greater than that associated with field exposure via feed (DEFRA 2005). The studies demonstrate that in cattle infected with BSE, the total amount of infectivity in the animal, as well as the distribution of infectivity in the animal's body, change over time (Wells, et al. 1994; 1998; 1999). The highest levels of infectivity were detected in the brain and spinal cord at the end stages of disease. Some cattle exhibited clinical signs of BSE as early as 35 months post oral exposure to the BSE agent. By 37 months post oral exposure, all five animals that were still alive demonstrated clinical evidence of BSE. Infectivity was found in cattle with clinical signs of BSE in the brain, spinal cord, dorsal root ganglia (DRG)³, trigeminal ganglia, and the distal ileum of the small intestine.

BSE infectivity was demonstrated in the brain, spinal cord, and DRG as early as 32 months post oral exposure to the BSE agent in some cattle (Wells, et al. 1994; 1998; 1999). Infectivity was demonstrated in these tissues three months before animals began to develop clinical signs of the disease. Infectivity was demonstrated in the distal ileum of cattle 6 to 18 months post oral exposure to the BSE agent and again at 38 months and 40 months post oral exposure.

As explained by DEFRA and by the European Commission's Scientific Steering Committee, a second phase of the pathogenesis studies, which uses a cattle bioassay as an endpoint, is being conducted to ensure that low levels of infectivity that may not have been detected in the first phase using the mouse bioassay are not missed (DEFRA 2005; EC SSC 2002b). This second phase of the study is still underway and is not expected to be completed for several more years. In the cattle bioassay, tissues from the same cattle orally exposed to BSE in the earlier pathogenesis studies, were injected directly into the brain of BSE-free cattle (DEFRA 2005). This method is considered to be several

³DRG are clusters of nerve cells attached to the spinal cord that are contained within the bones of the vertebral column. "DRG" as used in this document has the same meaning as the term "dorsal spinal nerve root ganglia." Trigeminal ganglia are clusters of nerve cells connected to the brain that lie close to the exterior of the skull.

hundred-fold more sensitive in detecting BSE infectivity than the mouse bioassay (DEFRA 2005). Preliminary results from the cattle bioassay study demonstrate that, in addition to the materials that were found to contain infectivity when the mouse bioassay was used, the tonsils of calves 10 months post oral exposure to the BSE agent also contain infectivity. However, because only one of five animals injected with tonsil material from infected animals developed clinical BSE at 45 months post-inoculation, the level of infectivity in the tonsils appears to be very low.

In addition to these studies on experimentally infected cattle, distribution of tissue infectivity has also been studied in cattle exposed to BSE under field conditions. In these animals, at the end stages of the incubation period with demonstrated clinical signs, BSE infectivity has been confirmed by mouse bioassay only in the brain, spinal cord, and retina of the eye (EC SSC 2001).

In a recent study, mice, genetically engineered to be highly susceptible to BSE and to overexpress the bovine prion protein, were inoculated with tissues from an end-stage clinically affected BSE-infected cow (Buschmann and Groschup 2005). The sensitivity of these mice to infection is significantly greater than other mice panels used in bioassays, and the sensitivity is even greater than that of cattle by approximately 10-fold. This study demonstrated low levels of infectivity in the facial and sciatic nerves of the peripheral nervous system, when injected into these highly sensitive mice. While these are interesting findings that can help further characterize the pathogenesis of BSE, they cannot be easily extrapolated into the context of the risk presented by natural exposure pathways. The findings may be influenced by the overexpression of prion proteins in these genetically engineered mice. Any apparent levels of infectivity are low in these extremely sensitive mice and would be even lower in other species such as cattle. Moreover, the route of administration to the mice was both intraperitoneal and intracerebral, both of which are very efficient routes of infection as compared to oral consumption. Given all of these factors, we conclude that there is not sufficient information in this study to alter our understanding of the epidemiologically significant distribution of BSE infectivity in cattle.

The amount and distribution of infectivity in specific tissues from an infected cow have been estimated by Comer and Huntley (2003) in their evaluation of the available literature. Those summary results, presented in Table 2, describe distribution of infectivity in various tissues, *i.e.*, brain, spinal cord, DRG, trigeminal ganglia, tonsil, and distal ileum, of a BSE-infected cow. The table uses an estimated weight of each tissue in grams, the number of estimated cattle oral infectious dose-50 (ID₅₀) units⁴ per gram, and the total number of cattle oral ID₅₀ units attributed to each tissue to estimate a percentage of cattle oral ID₅₀ units for each tissue.

⁴ BSE infectivity is expressed in terms of cattle oral infectious dose-50 units (ID₅₀). A cattle ID₅₀ is defined as the amount of infectivity required to cause infection in 50 percent of an exposed cattle population (Cohen et al. 2001).

Table 2. Infectivity in a clinical case of BSE (cattle oral ID₅₀)

Tissue	Weight g/animal	Infectivity		%
		ID ₅₀ /g	ID ₅₀ /animal	
Brain	500	50	25,000	60.2
Spinal cord	200	50	10,000	24.1
Dorsal root ganglia	30	50	1,500	3.6
Trigeminal ganglia	20	50	1,000	2.4
Tonsil	50	0.005	0.25	0.0
Distal ileum	800	5	4,000	9.6
TOTAL	1,600		41,500	

Source: Comer and Huntley 2003.

The table shows that 90 percent of the infectivity is associated with central and peripheral nervous system tissues, i.e., brain, spinal cord, DRG, and trigeminal ganglia. About 10 percent was associated with the distal ileum. Minimal infectivity was associated with tonsils in a clinically affected animal.

III. Release Assessment

In this section of the risk assessment we present evidence on the likelihood of each of the evaluated commodity groups to introduce BSE infectivity into the United States. To do so, we first evaluate the prevalence of BSE in Canada, using both quantitative and qualitative approaches. We then evaluate the specific risk reduction steps associated with each of the commodity groups: live bovines, blood and blood products, and small intestines other than the distal ileum. We also present numeric estimates of projected live bovine imports. We then combine the information presented in these sections to assess the release of BSE infectivity associated with each commodity group. All commodities are assessed qualitatively. In order to inform the quantitative exposure model described in Section IV.A., release of BSE via live bovines is assessed quantitatively, as well.

III.A. Estimation of BSE Prevalence in Canada

The purpose of this section is to estimate the prevalence of BSE in the adult cattle population of Canada. The detection of Canada's first native BSE case was confirmed on May 20, 2003. As of October 27, 2006, a total of nine BSE cases of Canadian origin had been confirmed in North America (CFIA 2006). This total includes a case of BSE that was confirmed in Washington State on December 25, 2003. By comparison, the UK had detected 184,453 cases of BSE through September 2006 (OIE 2006).

Prevalence is defined as the proportion of infected animals in a population. Although the simplest approach to the estimation of prevalence is to calculate this proportion directly (e.g., # identified cases/# samples tested), the limitations of current testing methodology for BSE make this approach less meaningful. Like many transmissible spongiform encephalopathies (TSEs), BSE has an incubation period of several years. Current technology can only detect the disease very close to the end of the incubation period, up

to 3 months before an animal begins to exhibit clinical signs. Therefore, infected but preclinical animals would not be detectable. The number of BSE cases detected through surveillance understates the disease prevalence because exposed animals may be incubating disease which would not always be detectable with current testing methodology. Furthermore, surveillance will miss a proportion of detectable (clinical or late incubation) cases. Therefore, statistical methods are applied to the available epidemiologic and surveillance data to estimate, with attendant uncertainty, the prevalence of BSE in Canada.

We have used two related, but distinct methods to estimate BSE prevalence in Canada (Attachment 1). Given its international prominence, we consider the European Union (EU) BSurvE model (Wilesmith, et al. 2004, 2005), recently developed for the purpose of estimating BSE prevalence in national herds. The BSurvE model is noteworthy for its sound epidemiologic structure, including stratifying cattle by age and cause of death and accounting for the relative likelihood of detecting BSE in various strata (EFSA 2004). The other prevalence estimation method used in this document, referred to as the Bayesian Birth Cohort (BBC) model, takes advantage of the BSurvE model structure to calculate BSE surveillance point values (random sample size equivalents) represented by targeted Canadian sampling of certain groups of cattle in which BSE cases are more likely to be detected. The BBC model adopts a Bayesian statistical framework to incorporate prior information about the decreased incidence of BSE observed in animals born after the initial ruminant-to-ruminant feed ban introduced in the UK in 1988. For the purposes of comparison and sensitivity analysis, the prevalence of BSE in Canada also is estimated using BSurvE.

The identical methodologies were used in the recently published and peer-reviewed U.S. BSE Prevalence document (APHIS CEAH 2006). The reviewers found that these models were statistically and epidemiologically sound.

III.A.1. BSurvE Model

We use as a basis for our prevalence estimates the “BSurvE” model developed in the EU (Wilesmith, et al. 2004). This model provides the benefit of combining surveillance data, population demographics, and knowledge of the disease pathogenesis with evidence of the relative likelihoods of infectivity in various sub-populations, to estimate BSE prevalence in the entire cattle population. Moreover, the prevalence estimate includes all infected cattle regardless of whether they are at a stage at which the disease is detectable.

Specifically, BSurvE stratifies cattle by age and cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) and accounts for the relative likelihood of detecting BSE in various strata. The model uses epidemiologic information of the disease that was accumulated during the UK and European outbreaks to predict parameters such as incubation period of BSE, probable length of an infected animal’s life, and the dynamics of disease expression in infected animals. It combines this information with the age distribution of a country’s national herd and its surveillance test data to achieve a set of point values for samples taken from cattle of different age and

cause of death strata called surveillance streams. The points represented by an animal tested for BSE are based on the relative likelihood that the disease would be detected in an animal leaving the herd at a particular age and by a particular surveillance stream. Under this scheme, one point is equivalent to an animal randomly selected for testing from the national herd (Wilesmith, et al. 2004). We obtain the BSE surveillance points used as inputs to the BSurvE prevalence estimation model using BSurvE Version 06.03. The BSurvE spreadsheet model and documentation are available on the BSurvE Web site (www.bsurve.com). The Web site includes updates made to the BSurvE model, documentation (Wilesmith, et al. 2004; 2005) that provides detailed description of the underlying functions of the model, and step by step user instructions.

III.A.2. Bayesian Birth Cohort Model (BBC): Inclusion of feed ban data

In order to halt the spread of BSE, all countries known to have had BSE cases have banned the feeding of ruminant protein to ruminants. Evidence gathered from countries, such as the United Kingdom, describes the decline in BSE cases following implementation of such feed bans (Schreuder and Wilesmith 1997). Therefore, Bayesian methods, which allow the combination of different types of information, can be used to incorporate this evidence with the surveillance data collected by a different country – in this case, Canada.

Because the provisions of the Canadian ruminant feed ban introduced in 1997 were comparable to or more restrictive than the UK feed ban in place from 1988 to 1994, we estimate the effect of a feed ban on BSE prevalence in Canada to be proportional to that observed in the UK during those years. The initial UK feed ban imposed in 1988 prohibited the inclusion of ruminant MBM in ruminant feed (DEFRA 2006c). In comparison, the Canadian feed ban prohibits the feeding of most mammalian proteins (with exceptions) to ruminants (CFIA 2002), and is therefore equivalent or more restrictive than the initial UK feed ban. In 1994, the UK requirements became more restrictive by prohibiting the use of any mammalian protein in ruminant feed. Additionally, U.S. veterinary epidemiologists reviewed records and conducted site visits to Canadian facilities to evaluate the efficacy of the Canadian ban and concluded that compliance with the feed ban was good, and that the feed ban was effectively enforced (USDA 2005). Although the degree to which the Canadian ban was able to reduce BSE transmission is difficult to measure directly, Cohen et al. (2001; 2003) concluded that the U.S. ruminant feed ban would rapidly decrease BSE prevalence following the ban even with a substantial initial infusion of infectivity. Since the U.S. and Canadian bans are similar to each other, it is reasonable to conclude that the findings of Cohen et al. (2001; 2003) would likewise apply to Canada.

The Bayesian Birth Cohort (BBC) model provides a more precise estimate of BSE prevalence in Canada by combining the epidemiologic theory underlying the BSurvE model with information about the effect of the feed ban on prevalence, as well as with surveillance data. Like BSurvE, the BBC prevalence estimate includes all infected animals in the standing adult cattle population of Canada, whether or not they are detectable and uses BSurvE's methodology for obtaining BSE surveillance points,

described above. As a starting point, the BBC model assumes that the BSE prevalence in cohorts born prior to the feed ban could range from 0 to 100 percent (i.e., the prior assumption was that prevalence is uniformly distributed between 0 and 100 percent). The prior assumption about prevalence is then modified with each iteration based on a constant prevalence before the feed ban, a decline after the ban proportionate to the UK, and the accumulated surveillance data. The model uses the total number of BSurvE points from each of the 1993-2004 birth cohorts that were tested by Canadian surveillance over a 7-year period ending August 15, 2006 as evidence for estimating the current prevalence.⁵ Prevalence of infected adult cattle alive on August 15, 2006 was estimated from the Bayesian model as the weighted sum of the individual birth cohorts' prevalence levels, where the weights are the proportion of infected animals born into each cohort that remain alive in August 2006.

The BBC model was implemented using two Bayesian analytical methods: Gibbs sampling and Sampling-Importance-Resampling (SIR). Gibbs Sampling is a Monte Carlo Markov Chain (MCMC) statistical method (Vose 2000). MCMC methods are based on an iterative updating scheme that is repeated until the sequence of parameter vectors converges. We first estimate the BBC model parameters by performing Gibbs Sampling using the WinBUGS statistical application Version 1.4.1 (MRC Biostatistics Unit 2004). Documentation for the WinBUGS application is available at www.mrc-bsu.cam.ac.uk. Using the same model structure and inputs, an alternative Bayesian method was used to verify the BBC model results obtained using WinBUGS. In contrast to the iterative Gibbs sampling method, Sampling-Importance-Resampling (SIR) is a noniterative Bayesian method. See the Prevalence document (Attachment 1) for details of the Bayesian Birth Cohort model, including the WinBUGS code and a description the SIR algorithm used to implement it.

III.A.3. Summary of assumptions and methods used in the Canadian calculations

Detailed explanation of the following assumptions and analytic methodology is included in Attachment 1.

1. As is true for many countries, precise data for age structure of the Canadian population is not known. However, the population structure was estimated based on data from Statistics Canada (<http://www.StatCan.ca>) and further verified by comparing the results with the age distribution predicted by the Harvard risk assessment for the U.S. population (Cohen et al. 2001; 2003). This distribution was then used for the “idealized” age distribution section of the BSurvE model.
2. BSurvE requires that the test data be stratified by age. However, prior to recent revisions to the OIE code (OIE 2006a), age stratification data were not an essential component of BSE surveillance, and thus were not routinely captured. In Canada,, age associated data are available, however, for approximately 50 percent of the BSE tests undertaken within CFIA's TSE network laboratories in

⁵ Under OIE Terrestrial Animal Health Code 2006 Appendix 3.8.4, BSE surveillance points remain valid for 7 years.

- 2004 and 2005. This subset represents over 20,000 animals. Considering the large number of animals with age data and that there appeared to be no significant differences in age related trends between these years, age stratification estimates for each surveillance stream was determined by pooling the two years of data. These estimates were then used to stratify the surveillance results of animals for which age data were not available.
3. The December 2003 case discovered in the United States was included in the prevalence calculation as a Canadian case, however, no other surveillance data for Canadian cattle in the United States were included. Thus, the positive data point was included but none of the corresponding negative results were considered in this analysis. The inclusion of positive but not negative data from the United States acts to over-estimate the prevalence estimate for Canadian cattle.
 4. BSE tests that were done as part of the epidemiologic investigations of BSE cases in Canada did not meet Canada's BSE surveillance criteria for the targeted sample population and were therefore excluded from the input data used to estimate the Canadian prevalence. Thus, only those samples that were collected for the purpose of Canada's BSE surveillance were included in the national prevalence estimate. Although the negative samples from healthy animals tested in the follow-up investigations were not used for estimating the prevalence of BSE in Canada, they do increase confidence that no unidentified cases are present in local association with the positive animals.
 5. Exit constants were set at the default of the BSurvE model which reflects the United Kingdom and European experience. These constants are primarily influenced by disease dynamics (BSurvE.com 2005) and are assumed to have minimal influence on North American assessments based on current knowledge of BSE.
 6. Clinical suspects were identified from the Canadian surveillance database based on the clinical signs and history recorded by field veterinarians in the submission record. They were not defined by "submission reason" because this category could allow samples to be designated as clinical suspect without supporting information from the veterinarian. Sample submission data that reported clinical signs listed on the CFIA Web site as compatible with the clinical suspect definition were electronically selected from the CFIA database. The selected records were further reviewed by BSE epidemiologists from CFIA and USDA to remove animals with acute neurological conditions or other diseases that explained alternate diagnoses for the neurological signs reported. The final set of samples were those that met criteria described in the OIE code for classification as clinical suspect animals.
 7. The initial UK ruminant feed ban substantially decreased the number of new cases in subsequent birth cohorts. Similar to the approach taken in estimating BSE prevalence in the United States (APHIS 2006), we assume that the Canadian feed ban during its first five years would reduce Canadian prevalence proportionately to the observed reduction in UK prevalence during the first five years of the UK ban: 1989 to 1994, during which the UK feed ban was most similar to the current

Canada feed ban. We therefore incorporate evidence from the UK reflecting the drop in prevalence following their feed ban into an estimate of Canadian BSE prevalence. We further note that as our knowledge of Canada's prevalence improves through continued surveillance efforts, the statistical contribution of the additional UK evidence diminishes.

8. Analysis of the Canadian BSE surveillance data provides no statistical basis for distinguishing BSE prevalence among birth year cohorts (Attachment 1). Therefore we calculated a single prevalence estimate for the entire population.

III.A.4. Results of prevalence estimation

The table below presents the expected prevalence estimates in the standing adult cattle population of Canada in 2006, as well as their respective 95th percent confidence levels. The BSurvE "Prevalence B" estimate is presented for comparison because it is calculated without incorporating evidence about the effect of the feed ban beyond that reflected in the surveillance data. See Attachment 1 for details of the BSurvE model and inputs.

Table 3. Results of prevalence calculation.

Prevalence in adult population	Bayesian birth cohort method (BBC) with UK feed ban data	BSurvE Prevalence B estimate without including feed ban data
Expected value (mean)	0.68×10^{-6}	3.9×10^{-6}
95 th percent confidence level	1.1×10^{-6}	6.8×10^{-6}

III.A.4.a. *Application of Prevalence Estimates to the Exposure Assessment*

It is important to note that the estimated prevalence distribution presented here represents parameter uncertainty. For a fixed prevalence value, the number of infected cattle in the population would still vary randomly over time. Assuming a constant probability of infection, the random variability in the number of BSE infected animals in the adult cattle population would follow a binomial distribution. For a large sample size and low prevalence values, the Poisson approximates the binomial variability distribution and is incorporated in the model supporting the exposure assessment for live bovines (Section IV.A. and Attachment 2) to represent variability around the prevalence estimates generated here.

Moreover, it is important to recognize that our models provide a robust estimate of the prevalence in Canada at this point in time. They do not project changes in prevalence expected in the future. Empirical evidence from the UK has demonstrated and simulation studies have reinforced that implementation of a ruminant to ruminant feed ban leads to continued decrease in prevalence over time (Cohen, et al. 2001; 2003; DEFRA 2006, EC 2003; 2005), yet the methods we use to estimate the prevalence of BSE in Canada cannot predict such future changes in prevalence. We can, however, use these August 15, 2006 prevalence estimates in two different ways. First, we can use them to provide a current

estimate of possible release via live animal imports in the first year of our analysis, and we can qualitatively consider subsequent years of decreasing prevalence in our exposure assessment. Second, as we allow for less likely outcomes over the 20 year period of the analysis, we can also use these prevalence estimates as numeric surrogates for the release input parameter of the exposure model (Attachment 2) which we use to inform our exposure assessment (Section IV.A.).

Like the effects in the UK described in the Hazard Identification (Section II), similar effects of a feed ban have been seen in the EU. The apparent number of cases of BSE identified in the EU-15 Member States has decreased every year since 2001. Feed ban legislation was initially adopted within the EU in August 1994, and was gradually strengthened over the intervening years until the current requirements took effect in 2001. While the legislation took effect upon publication in 1994, it is recognized that initial implementation was inconsistent and some efforts were not immediately effective. In fact, this initial inconsistency, especially regarding cross-contamination, led to increasingly stringent feed ban requirements (EC 2003; 2005). Nevertheless, the implementation of active surveillance efforts within the EU in 2001 documents the effects of the initial feed ban. Allowing approximately 5-6 years before being able to observe the effects of the feed ban on diagnosed cases, the decreasing number of bovine cases reflects the impact of the initial feed ban. An alternative way to evaluate the effects of the feed ban is to observe the number of cases by year of birth. In the EU, the peak number of cases was born in 1995 followed by a significant drop, reflecting the effect of the feed ban (EC 2005a).

Given this demonstrated experience regarding the effects of a feed ban, it is extremely likely that the prevalence of BSE in Canada will continuously decrease over the next several years. The Canadian government has reached the same conclusion in their analysis and further predicts the ultimate eradication of the disease (CFIA 2004; 2006). Therefore, we conclude that it is highly probable that the prevalence will continue to decrease from the currently low level estimated here.

III.B. *Release of infectivity via the various commodities proposed for importation from Minimal Risk Regions*

III.B.1. Release of BSE infectivity via live bovines

The OIE establishes standards for the international trade in animals and animal products. The OIE *Terrestrial Animal Health Code* (Chapter 2.3.13) allows trade in live cattle from regions that have reported BSE and have an effective feed ban in place, provided that the cattle were born after the date when the feed ban was effectively enforced.

As described in the Hazard Identification section of this document, BSE is spread under field conditions when cattle consume feed contaminated with the BSE agent. Transmission can be prevented by excluding potentially infected materials from ruminant feed. Therefore, bovines born after the date when a ruminant-to-ruminant feed ban was effectively enforced are unlikely to have been exposed to the BSE agent.

Although the proposed rule addresses the importation of live bovines, we acknowledge that a very small proportion (roughly 2500 of 1.3 million, or 0.2 percent as discussed in Section III.C.) of these animals will be bison. Therefore, we focus this discussion on the impact of the “date of the effectively enforced feed ban” mitigation on cattle, rather than on bovines in general. We have no reason to believe that these conclusions do not also apply to bison, however.

In the sections that follow, we discuss the feed ban and related activities in Canada that mitigate the risk that cattle exported from Canada to the United States would be exposed to the BSE agent. Then, in order to increase the certainty that animals eligible for import to the United States have been subject to the fully implemented Canadian feed ban, and to be consistent with the OIE standard described above, we apply the gathered evidence to determine the date when we are confident that an effectively enforced ban was achieved.

As part of previous rulemaking, an evaluation was done that concluded that the feed ban was effectively enforced (APHIS 2004). This conclusion was based on consideration of the regulations in place based on statutory authority, adequate infrastructure to implement the regulations, and evidence of implementation and monitoring (i.e., compliance inspections, training and records).

After this determination has been made, then consideration can be given to when full implementation is achieved. Full implementation and effective enforcement would be achieved after completion of the initial (or practical) implementation period and sufficient time has elapsed to allow most feed products to cycle through the system. The practical implementation period, which begins when the regulations are initially put in place, can be determined by evaluating implementation guidance and policies, such as allowing grace periods for certain aspects of the industry. In addition, the time necessary for initial education of industry and training of inspectors must be considered. After the practical implementation period is defined, then we considered a sufficient time period subsequent to this to allow most feed products to cycle through the system, given the management practices in the country.

Based on this evaluation, APHIS concludes that cattle born in Canada on or after March 1, 1999 can be imported into the United States with a very low risk that they have been exposed to the BSE agent.

III.B.1.a. *Feed ban in Canada*

In 2004, USDA conducted a risk analysis to evaluate the BSE risk from ruminants and ruminant products imported from regions presenting a minimal BSE risk, and to evaluate whether Canada can be classified as a minimal risk region (APHIS 2004). As part of the risk analysis, USDA evaluated a series of measures introduced in Canada to prevent the feeding of ruminant proteins to ruminant animals. USDA considered the compliance activities reported by the CFIA as well as epidemiological information as evidence of the effectiveness of the feed ban. The risk analysis concluded that compliance with the feed ban was good, and that the feed ban was effectively enforced.

In response to the detection of two additional BSE cases in Canada, in January 2005, USDA reassessed the oversight of Canada's feed ban. Based on review of inspection records and on-site observations, USDA confirmed that Canada has a robust inspection program, that overall compliance with the feed ban is good, and that the feed ban is reducing the risk of transmission of BSE in the Canadian cattle population (USDA 2005).

In addition to the USDA audit of the Canadian feed ban, CFIA conducted its own review in 2005, and concluded that the ban is providing an effective barrier that is contributing to reducing the BSE risk in the country to an extremely low level (CFIA 2005).

Canada's feed ban was also a central issue in an investigation conducted by the USDA in 2005 of the epidemiology of BSE in North America (USDA 2005a). In 2006, Canada released the assessment of the North American cases of BSE diagnosed from 2003 to 2005 (CFIA 2006). This report describes the epidemiological investigation of cases as well as their association with potential sources of infectivity. Information from the epidemiological investigations to date and the 2005 feed ban reports are incorporated into the elements of our discussion below regarding the efficacy of Canada's feed ban.

In June 2006, CFIA finalized regulatory amendments to enhance their feed ban. These require, among other things, the removal of specified risk materials from all animal feeds, pet food, and fertilizer. These regulations will not be effective until July 12, 2007, and therefore they are not considered in the following discussions.

III.B.1.a.1. *Implementation of the Feed Ban*

On August 4, 1997, Canada issued regulations prohibiting the use of mammalian protein in ruminant feeds as follows: "Any feed that is, or that contains any prohibited material originating from a mammal (with exceptions) shall not be fed to a ruminant" (CFIA 2002; Health of Animals Regulations, Part XIV, Sections 162-171). The ban provided exceptions for milk, blood, gelatin, and protein derived solely from porcine or equine sources. Canadian feed regulations also prohibit the use of plate waste⁶ and poultry litter in ruminant feed. Canada's feed ban prohibits feeding of most mammalian proteins to ruminant animals, such as cattle, sheep and goats.

Elements of the feed ban include requirements for labeling and record-keeping. Feeds for equines, porcines, chickens, turkeys, ducks, geese, ratites or game birds, containing prohibited materials, must be clearly labeled with the following cautionary statement, "Do not feed to cattle, sheep, deer or other ruminants." Labels for bulk feed are stapled to the invoice and shipping documents. Ruminants may be fed pure porcine meal, equine meat meal and nonmammalian protein meal (fish, avian), as well as milk, blood, gelatin, rendered animal fat and any products produced from these materials from all species.

⁶ Plate waste means any edible material originating from kitchens, restaurants, catering facilities or the household of the farmer or person tending the animals.

Feed manufacturers, renderers, retailers, and livestock producers must document their production procedures and feeding practices to verify their compliance with the feed ban. Feed manufacturers must keep records regarding the composition, identity, and distribution of all feeds for the species named in the regulations. Renderers, feed manufacturers and farmers must take steps to prevent the incorporation or cross-contamination with material prohibited under the feed ban into ruminant feed. To prevent the misfeeding of prohibited material to ruminants, users of livestock feed must keep labels or invoices from all purchased feeds containing prohibited material; these records must be kept for two years. Prohibited material may be fed to non-ruminant animals such as poultry and swine. CFIA expected that these practices and requirements would become more efficient and familiar over time as evidenced by the phase-in periods described below.

Beginning as early as 1996, as the ban was being formulated, government officials in Canada met extensively with feed mills and the rendering and livestock industries to educate and inform all sectors about the upcoming regulatory requirements (CFIA 2005). As noted above, Canada published its regulations banning prohibited material in ruminant feed on August 4, 1997.

Although the regulations came into force the same day, full implementation was a gradual process. From the outset, CFIA recognized that a phase-in period would be required before prohibited materials that were already in feed channels would be exhausted, and labeling and record keeping requirements would be met. It was estimated that it would take approximately 30 days for feed mills and retailers to use up and distribute existing supplies of “old” product (i.e., unlabeled feed intended for ruminants and produced using ruminant MBM); 60 days to add the caution statement to labels, invoices, and production records; and 60 days for farms to use up their stores of “old” product (USDA 2005a). All retailers were given until September 3, 1997 to use or distribute feed already produced. Feed manufacturers received a grace period until October 3, 1997 to comply with labeling requirements. Livestock producers were given a grace period until October 3, 1997 to use the feed manufactured and purchased prior to the feed ban. However, feed tracing associated with the epidemiological investigations of one of the Canadian BSE cases suggested that feed produced prior to implementation of the feed ban may have been available at feed stores and/or on-farm several months longer than anticipated. Therefore, CFIA considered that the “practical implementation period” may have been up to 6 months after the date of the ban (USDA 2005a).

Implementation of the feed ban required addressing the four major components of the feed chain involving the use of ruminant derived proteins in animal feeds, and preventing cross contamination of cattle feed with prohibited material or misfeeding of prohibited material to cattle. Briefly, these components are the collection of inedible products from slaughter and/or dead stock and transport of these materials to the rendering plant; processing by the rendering plant of inedible material into products (primarily MBM) and transport to feed mills; mixing by the feed mill of the rendered products with grains and other ingredients into feeds for a variety of animals (the highest volume being used in feed for poultry); and distribution to farms where these feeds may be used with or

without further mixing. Specific control measures appropriate to each of these components had to be developed and incorporated into the feed ban requirements.

III.B.1.a.2. Rendering industry

The rendering industry is crucial in reducing the risk of transmitting BSE infectivity, not only because of its role in inactivation of the BSE agent, but also because it serves as a critical control point for the redirection of ruminant protein away from cattle feeds. Since 1998, all Canadian rendering facilities have been subject to annual inspections and permitting (USDA 2005). Three types of permits are issued, allowing companies to produce only non-prohibited material, only prohibited material, or both non-prohibited and prohibited material (USDA 2005). Permitting requires implementation of manufacturing controls (such as Good Manufacturing Practices and risk-based HAACP⁷), record-keeping (for both production and distribution) and labeling requirements (“Do not feed to cattle, sheep, deer or other ruminants” on labels and invoices for all prohibited material) directed at preventing cross-contamination or misfeeding.

III.B.1.a.3. Addressing cross-contamination

As mentioned earlier, renderers, feed manufacturers and farmers must take steps to prevent cross-contamination of ruminant feed with material prohibited under the feed ban. Such contamination can be prevented by having dedicated processing lines or facilities which use only prohibited or non-prohibited material. If a facility handles both prohibited and non-prohibited material, procedures must be established and maintained to conduct flushing and/or clean-out between batches of product to prevent cross-contamination.

Investigation of the BSE cases born in 2000 and 2002 suggest that these animals were most likely exposed during their first year of life to feed contaminated during processing (CFIA 2006b). In particular, the reports of the investigations identified incidents of concern in which ruminant feed was processed or transported immediately following the processing of non-ruminant feed containing prohibited material. Such incidents were in contravention of Canadian regulations, which require flushing and/or clean-out between batches if ruminant feed is processed on the same lines as feed containing prohibited material.

The detection of BSE in an animal born after the date the feed ban was implemented does not indicate an overall failure of the measures in place to reduce and eventually eradicate the disease from a country. In most other countries that have experienced cases of BSE, similar events have occurred. Nevertheless, despite such occurrences, a feed ban will be effective in decreasing the transmission of disease (Heim and Kihm 2003).

The feed industry has taken a number of aggressive steps to comply with measures in the feed ban designed to reduce the risk of cross-contamination of feed for cattle with

⁷ HAACP is the frequently used acronym for Hazard Analysis Critical Control Point, an approach to controlling hazards, such as food contaminants, in the manufacturing process.

prohibited material. Recently, both the United States and Canada reviewed the changes made to industry procedures and government inspectional oversight to meet the feed ban requirements at feed mills and rendering facilities (USDA 2005; CFIA 2005). These reviews demonstrated, for example, that the rendering industry has moved toward establishment of dedicated facilities or dedicated processing lines within rendering facilities (USDA 2005; CFIA 2005). Of the 29 rendering facilities in Canada, six handle both prohibited and non-prohibited material. Of those six, four use dedicated processing lines (CFIA 2005). According to CFIA's reports, the feed manufacturing industry has also moved toward dedicated feed manufacturing facilities. Per the most recent review, 94 (17 percent) of the 550 commercial feed mills that handle prohibited material also manufacture feeds for ruminants (CFIA 2005). These actions, in addition to the labeling and record keeping requirements for all products containing prohibited material, decrease the likelihood of contamination of ruminant feeds with prohibited material. HACCP programs, certified through the Animal Nutrition Association of Canada, have been developed and implemented at commercial feed mills producing over 60 percent of total commercial feed production (McGrath 2004). Under these programs, feed mills have incorporated elements of the feed ban into their manufacturing process that are supported by additional training of employees, developing standard operating procedures, and maintaining appropriate records.

III.B.1.a.4. Education and industry awareness

The Canadian federal government, through the CFIA, is responsible for regulating and overseeing inspection of the animal feed industry. CFIA developed education and training initiatives shortly after the feed ban was first proposed in 1996 and began educating their own inspection force, as well as the feed industry, livestock producers, and veterinarians about the impending regulations and the steps necessary to implement them. The Feed Program Inspection Manual, the main training tool for CFIA inspectors, was supplemented with newly developed guidelines, standards and procedures to facilitate uniform implementation of the new feed ban inspection tasks. Inspections were increased. Workshops were held in all regions to cover the controls and processes required to comply with the feed ban's requirements (CFIA 2005).

Once the feed ban regulations were in place, CFIA continued to interact with and educate feed manufacturers, renderers, feed retailers, and producers to support implementation of the new regulations. These efforts included workshops; posting the new regulations on the CFIA Web site; and preparing and disseminating bulletins and press releases to all affected parties. Broad educational outreach by CFIA about BSE was made to government and private veterinarians, provincial, federal and university diagnosticians, producers, and workers involved in all aspects of the livestock industry (CFIA 2005). The cumulative effect of these educational efforts has been to support and enhance the effectiveness of the feed ban by ensuring that each sector of the impacted industry has taken the steps necessary to implement and sustain an effective feed ban, understand the impact of BSE on Canadian agriculture, and eliminate exposure of the Canadian cattle population to BSE infectivity. It is likely that the high level of awareness fostered by CFIA at various levels facilitated the effective implementation of the feed ban.

III.B.1.a.5. Inspections and compliance

Once the new feed regulations had been introduced, communications with the affected industries broadened and CFIA implemented an inspection program. This program was introduced in phases. From 1997-2000, inspection activities focused on integrating the feed ban's requirements into standard industry practices. For example, since 1998, rendering facilities were required to pass an annual inspection in order to renew their permits to operate. In 2000 and 2001, CFIA modified its compliance programs by increasing the frequency of inspections of commercial feed mills from once every three years to every year and by continuing the annual inspection and permitting of all rendering facilities. Since 2002, CFIA has been conducting annual inspections of all rendering and commercial feed mill facilities and some ruminant feeders and retail feed distributors. There are approximately 20 feed mills per renderer and 400 livestock producers per feed mill. Because of the impact of each renderer or feed mill on so many producers, measures implemented by CFIA to prevent commingling or cross contamination of ruminant feed with prohibited materials directed at the rendering and feed manufacturing industries were essential for implementation of an effective feed ban. USDA has concluded that, in combination with labeling and record keeping requirements, these measures have continued to serve to prevent feeding of prohibited protein to cattle (USDA 2005).

III.B.1.a.6. On-farm feeding practices contributing to feed ban efficacy

To evaluate the implementation and effectiveness of the feed ban at the farm level, it is important to consider on-farm feeding practices. Most Canadian cattle are raised on either dairy farms or beef cattle operations. The nutritional requirements of dairy and beef cattle differ, and the nutritional needs of each vary by age and stage of production. Animal source proteins may be useful in the rations of dairy cattle to balance specific nutrients (lysine and other amino acids, calcium, and phosphorus) and supplement protein intake. However, a variety of plant proteins and animal protein alternatives from non-prohibited sources are available to Canadian producers including fish meal, porcine blood meal, feather meal, and processed soy products. Most cattle producers do not hold extensive long term inventories of purchased feeds on their farms due to limited storage space and expense. These practices make it unlikely that feeds containing prohibited material were available for more than a few months after the original implementation of the feed ban. The possible exception is mineral mixes produced before the feed ban that may have contained ruminant meat and bone meal. Mineral mixes are typically fed daily but in very small quantities (grams rather than pounds per day) (NRC 2001; NRC 1996) and may be stored on the farms for longer periods of time. We believe, however, that they are not likely to have been purchased for use for periods longer than a year.

Both beef and dairy cattle production can be considered to have an annual or 12-month cycle, in that a cow on a beef or dairy farm will generally give birth once a year. Calving

occurs year-round on Canada's dairy farms to ensure a constant supply of fluid milk and the farms typically raise their own replacement heifers. Most dairy farms produce their own forage and grains (CFIA 2002). Forages produced seasonally are stored on the farm to provide the basis for the diet fed to dairy cattle of all ages and production stages. Protein supplements and specialty feeds, such as mixed calf feeds, are typically purchased commercially in quantities to be fed out over a few months because these supplemental feeds are expensive to purchase, costly to store, and may deteriorate with time. Typically, purchased feeds are available throughout the year with only moderate price variations, so there is little incentive for producers to maintain large on-farm inventories (Leger 2005 personal communication). The Canadian beef production cycle is very seasonal in that cows are bred so that calving occurs at the same time of year, general in the spring (CFIA 2002). Producers are not likely to carry extensive feed inventories from season to season (Gow 2005 personal communication). Therefore, in both dairy and beef production, a 12-month period would generally be sufficient to allow purchased feed products that may contain MBM to be completely used.

III.B.1.b. *Conclusions: Infectivity release via importation of live bovines*

In its previous risk analysis (APHIS 2004), APHIS concluded that, at the time the analysis was conducted, Canada had an effective feed ban in place. However, that analysis did not attempt to establish a specific date on which the ban became effective. The feed ban comprises a number of interrelated measures that have a cumulative effect, and compliance with these measures continues to increase as the program evolves. In addition, since the implementation of the feed ban on August 4, 1997, CFIA has continued to revise and strengthen its processes and procedures to further enhance the effectiveness of the feed ban. APHIS concludes that all of these factors have resulted in an incremental reduction in the risk that Canadian cattle will be exposed to the BSE agent.

As discussed above, a "practical implementation period" of six months has been estimated for the feed ban to be fully implemented, making February 1998 a more realistic date on which the ban can be considered to have gone into effect. The likelihood that cattle born after that date would be exposed to the BSE agent decreases even further over time. APHIS considers that a period of one year following the full implementation of the feed ban allows sufficient time for the measures taken by Canada to have their desired effect. Therefore, APHIS concludes that cattle born on or after March 1, 1999 are unlikely to have been exposed to the BSE agent via feed and can be imported into the United States for any purpose with a very low risk that they will be infected with the BSE agent.

III.B.2. Release of BSE infectivity via blood and blood products.

APHIS proposes that blood and blood products from Canadian bovines be allowed to enter the United States under certain conditions. This section evaluates the likelihood of introduction of BSE into the United States via these commodities, assuming the implementation of several required mitigations listed here. The blood and blood products

must be from a clinically normal animal and, if harvested at the time of slaughter, the animal was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity or to a pithing process. For fetal bovine serum (FBS), the mitigations are that the dam must pass ante-mortem inspection, the uterus must be removed from the dam's abdominal cavity intact and taken to an area separate from the kill floor for collection. All blood must be collected in a closed system.

Following the risk assessment format described in the Introduction, in this section we analyze the various nodes in the potential risk pathway for imported blood and blood products from Canada. We first provide justification for focusing our discussion on those products used in the production of veterinary vaccines and drugs. In keeping with the scope of this risk assessment, we are addressing only those pathways that may influence animal health⁸. The impact of BSE prevalence in Canada on the overall likelihood of release of infectivity into the United States will be integrated with the findings of this section in the release summary described in Section III.D.2.

III.B.2.a. *Scope of the analysis: relevant products*

Blood and blood products can be divided into two main groups: whole blood and cellular derivatives such as red cell concentrate, platelets, and other cellular elements; and plasma-derived products including serum (including FBS), clotting factors, immunoglobulins and albumin (Farshid, et al. 2005). Plasma is the cell-free portion of the blood. Serum is plasma with fibrinogen and clotting factors removed.

Because blood and blood products (or products manufactured with them) are typically delivered by injection, they present different risks than most other bovine products considered for import. Injection presents a different risk pathway than does oral consumption of BSE-contaminated bovine materials. The latter pathway is commonly evaluated in the cattle BSE literature. The route of exposure can affect the risk of disease transmission. The relative efficiencies of transmission have been reported to be, in decreasing order, intracerebral (IC), intravenous (IV), intraperitoneal (IP), subcutaneous/intramuscular (SC/IM), and oral/intragastric. In mouse scrapie models, it is estimated that the subcutaneous/intramuscular route requires 10,000 times the intracerebral dose required to produce infection (Prince, et al. 2003). The equivalent of 100,000 IC doses is thought to be necessary for infection by the oral/intragastric route (Prince, et al. 2003). We extrapolate from these data that mice exposed to scrapie via the IM or SC routes are 10 times more likely to become infected than those exposed orally. Therefore, we limit this assessment to the pathways in which these products can be used in animal vaccines and injectable drugs.

Of the various products listed above, only plasma-derived fetal bovine serum (FBS), also called fetal calf serum (FCS), and bovine serum albumin (BSA) derived from adult and calf serum are used in significant amounts for the preparation of animal vaccines and drugs. Other products that could theoretically be used in the manufacture of animal drugs

⁸ The accompanying environmental assessment (APHIS 2006) must consider potential impacts of a proposed action on the human environment, including public health.

include cell-derived components such as hemin, hemoglobin, lymphocytes and platelets; and plasma-derived products, such as blood lipids, bovine immunoglobulins, clotting factors, cytokines, fibronectin, Fractions I-V (various proteins separated from plasma), hormones (e.g. serum gonadotropin), iron, and plasma protein (Popek 2005 personal communication). In practice, however, these items are not used in the manufacture of animal vaccines and drugs, limiting their role in the potential BSE risk pathway for animal exposure.

III.B.2.b. *Infectivity of blood and relevant blood products*

Experiments based on primary infection by the oral route have examined tissues from BSE-infected cattle. Although infectivity was identified in various tissues, primarily in the central nervous system, it was not demonstrated in a wide variety of other tissues. Specifically relevant for this discussion is the fact that no BSE infectivity was demonstrated in cattle blood or any tested derivatives (EC SSC 2002). This conclusion derives from studies in which tissues from infected cattle were injected intracerebrally (IC) and intraperitoneally (IP) into mice (the “mouse bioassay”), or IC into cattle (the “cattle bioassay”). Mouse bioassays were performed using buffy coat (the white cell fraction of centrifuged whole blood), clotted blood, fetal calf blood and serum from confirmed clinical cases (Kimberlin 1996 cited in EC SSC 2002). Mouse and cattle bioassays were performed on buffy coat from cattle experimentally exposed orally to the BSE agent. In all cases, no evidence of infectivity was detected.

Because no evidence of infectivity has been found in cattle blood or the components listed here, we could end this portion of the release assessment at this point. However, we acknowledge that the route of exposure – injection vs. oral consumption – warrants further consideration. We also recognize that additional processing steps may have further mitigative effects, and therefore, should be presented. However, presenting direct evidence for the effects of processing of bovine blood on the persistence of BSE infectivity is not possible because infectivity is not detectable even in unprocessed bovine blood. Thus, although APHIS generally avoids extrapolating from studies of TSEs in other species, in order to utilize the only available evidence, we have elected to incorporate such information here. Thus, we cautiously use studies on TSEs in other species as potential indicators of the behavior of BSE in cattle blood if it were to be present in previously undetectable levels.

Investigators have demonstrated that BSE can be transmitted to sheep by transfusion of whole blood from sheep experimentally infected with BSE (Houston, et al. 2000; Hunter, et al. 2002). In these studies, a transfusion of 400 ml of whole blood, taken from clinically normal infected sheep, caused disease in 2 of 24 recipients. Blood or buffy coat taken from clinically ill animals, however, did not cause disease in the 4 recipients. These same investigators also examined scrapie in sheep. A total of 4 sheep out of 21 transfused with blood from sheep naturally infected with scrapie developed disease. The transfusion of buffy coat derived from a clinically ill animal caused disease in the recipient. The Scientific Steering Committee of the European Commission examined

these studies and their implications. They concluded that the finding of infectivity in the blood of sheep could not be extrapolated to BSE in cattle (EC SSC 2002a).

Brown, et al. (1999) using a human strain of TSE (Gerstmann-Straussler-Scheinker, or GSS) in mice inoculated intracerebrally, concluded that infectivity was present in the buffy coat (platelets, white cells) during the preclinical phase of TSE, but absent or in only trace amounts in the plasma or plasma fractions. Following the onset of clinical signs, increased infectivity of both buffy coat and plasma was found, but still very low compared to levels in the central nervous system. As cited in a review of the relevant literature (Comer 2004, p. II.18), most studies using a rodent model and adapted strains of scrapie or CJD demonstrated that the fractions containing white blood cells have the highest levels of infectivity.

In contrast to investigations of the natural distribution of infectivity in rodent blood fractions, one “spiking” study added high levels of hamster-adapted scrapie infectivity from brain homogenate to normal human blood. Following fractionation by centrifugation into red cells, white cells/platelets, and plasma components, titrations indicated that the majority of infectivity was in the red cell component (Brown, et al. 1998). These results, although not as relevant to understanding the natural distribution of TSEs in blood, may potentially apply to the distribution following cross-contamination at blood collection. Therefore, if contrary to current research, or if the proposed mitigations are not properly implemented, any BSE infectivity is present in bovine blood, either naturally or via cross-contamination, it would likely be highest in the cellular components. These fractions, both red and white cells, are excluded when harvesting FBS and BSA used in the preparation of vaccines and drugs.

Further decrease in TSE infectivity occurs with fractionation of plasma proteins. Fractionation is the process whereby specific proteins, such as albumin, are separated out from other components of the plasma. Infectivity in various fractions has been examined. For example, using data from several cited studies Comer (2004) estimated that human albumin contains 3.1×10^{-5} vCJD ID₅₀/gram. Compared to Comer’s estimates of infectivity in whole blood (2 iv vCJD ID₅₀/gram), this figure represents a dramatic decrease.

In conclusion, the available evidence indicates that TSEs in other species, when found in the blood, are localized primarily to the cellular fractions. Although BSE has never been detected in any bovine blood or blood product, we expect even further risk reduction after removal of cellular fractions in the preparation of the most commonly imported bovine blood commodities.

III.B.2.c. *Likelihood of maternal transmission of BSE*

As discussed in Section II.A. of the Hazard Identification portion of this document, the likelihood of maternal transmission is extremely low. Therefore, for FBS and other fetally-derived products, maternal transmission represents an additional risk-reduction step. If, despite evidence to the contrary, maternal transmission of BSE were to occur,

infectivity is unlikely to localize to the fetal blood, just as it is unlikely to localize to adult blood.

III.B.2.d. *Proposed mitigations to prevent contamination at collection*

Although we have demonstrated that BSE infectivity is not likely to localize to the adult or fetal blood, we recognize the possibility of cross-contamination with infective tissues, or SRMs at the time of collection, particularly in a slaughter environment. Certain slaughterhouse stunning practices – specifically the use of devices that inject compressed air or gas into the cranial cavity or pithing processes - may introduce macro-emboli of CNS tissue into the circulatory system (Anil et al., 1999; Schmidt et al., 1999). In addition, collection of blood in an open manner may allow other tissues to contaminate the blood. For example, pieces of spinal cord or other risk tissues could fall into an open container, such as a bucket or tub, if collection and pooling of blood from several animals is done in a slaughterhouse environment.

In order to prevent contamination due to such potential sources of infectivity, APHIS proposes the following mitigations:

For all blood:

1. the blood is collected in a closed system.

For blood collected at slaughter, the slaughtered animal:

2. must pass ante-mortem inspection and
3. was not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process

For fetal bovine serum:

4. the dam must pass ante-mortem inspection and is not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process
5. the uterus is removed from the dam's abdominal cavity intact and taken to an area separate from the kill floor

For blood collected from live donors:

6. the donor must be free of clinical signs of disease

Based on the evidence presented above, we conclude that bovine blood is highly unlikely to contain BSE infectivity, the fractions that are likely to be commercially exported are highly unlikely to contain infectivity, and that USDA-specified mitigations will prevent cross-contamination.

III.B.3. Release of BSE via small intestine other than distal ileum.

In this section we qualitatively assess the likelihood of BSE infectivity being introduced into the United States via the importation from Canada of bovine small intestine other than the distal ileum. We address this likelihood by considering the various steps, or nodes, in the risk pathway. These nodes include the distribution of infectivity to the

small intestines, and mitigations to ensure proper removal of the potentially infectious distal ileum.

III.B.3.a. *Infectivity of the small intestine*

The evidence presented below demonstrates that the only portion of the cattle intestine in which BSE infectivity has been found in any assay is the distal ileum. We describe the most relevant observations regarding the pathogenesis of BSE in the gastrointestinal system of cattle experimentally and naturally exposed to the BSE agent.

- Pivotal studies of the BSE agent include experimental investigations of the pathogenesis of BSE after oral exposure of cattle. The experimentally exposed animals received a dose of infectivity that was 10 to 100 times greater than most cattle that have been naturally exposed via contaminated feed. In these studies, investigators examined the distribution of the agent in the lymphoreticular system, the peripheral nervous system, the central nervous system, striated muscles, and major viscera at various times after exposure (Wells, et al. 1996). Infectivity in bovine tissues was first assayed in the mouse bioassay, a procedure in which the agent is injected intracerebrally and intraperitoneally into certain nontransgenic strains of mice (Wells, et al. 1996; 1998) which are then observed for development of clinical signs. Results from the mouse bioassay demonstrated infectivity in the distal ileum of cattle from 6 to 18 months and from 36 to 40 months after oral exposure. No infectivity was detected at any time in the esophagus, reticulum, rumen, abomasum, proximal small intestine, proximal colon, distal colon, and rectum (EC SSC 2002b). In later studies, the same tissues were assayed for infectivity by intracerebral inoculation of cattle, a more sensitivity assay method (EC SSC 2002b). The cattle bioassay confirmed that the agent could be recovered only from distal ileum at times previously reported in the mouse bioassay.
- Studies examining the distribution of PrP^{Sc} by immunohistochemistry⁹ in the distal ileum of infected cattle confirmed that PrP^{Sc} accumulated in Peyer's patches of the distal ileum at 6, 10, 14, 18, 36, and 40 months after exposure (Terry, et al. 2003). These findings were consistent with results from the mouse bioassay.
- No PrP^{Sc} was detected by immunostaining in the duodenum, jejunum, cecum, colon, myenteric plexus, and submucosal plexus of calves orally exposed to large doses of the BSE agent and killed 6 months after exposure (Terry, et al. 2003). In contrast, immunostaining of follicles from Peyer's patches of the distal ileum did reveal the presence of PrP^{Sc} in these same calves.

⁹ We note that detecting the presence of PrP^{Sc} is not the same as demonstrating infectivity. There are many variables that contribute to infectivity, and while detecting PrP^{Sc} may indicate that infectivity could be present, it does not, by itself, indicate that it is indeed present.

- The distal ilea of 29 naturally occurring cases of BSE were examined for PrP by immunohistochemistry. Sparse PrP^{Sc}-specific immunostaining was observed in neurons of the myenteric plexus of the distal ileum of nine of the cattle. No immunostaining in the submucosal plexus of the distal ileum of any of the infected cattle was observed, suggesting a very low level of infectivity in the enteric nervous system in the clinical phase of BSE (Terry, et al. 2003).

In summary, BSE infectivity has been found in the distal ileum of experimentally exposed cattle and not in other sections of the intestine. In addition, in naturally occurring cases, sparse immunostaining has been observed in the myenteric plexus of the distal ileum. Since the myenteric plexus extends throughout the small intestine, we acknowledge the possibility that infectivity might exist in the myenteric plexus of the jejunum or the duodenum. However, if infectivity in intestinal tissues (other than distal ileum) exists, it is below the level of detection by both the mouse and cattle bioassay. Given the relative efficacies of these experimental modes of transmission compared to oral exposure at doses estimated to have occurred in the field, we conclude that intestine other than the distal ileum is highly unlikely to contain epidemiologically-significant levels of infectivity, if any infectivity is present at all.

III.B.3.b. *Likelihood of improper removal of the distal ileum*

As discussed above, the distal ileum is the only portion of the bovine intestine in which BSE infectivity has been found in experimentally and naturally infected cattle. Although infectivity has not been detected in the rest of the small intestine, the complete removal of the distal ileum is essential to ensure that imported bovine intestine does not include a potential source of BSE infectivity. In this section we describe the anatomic relationships between the relevant parts of the bovine intestine and the mitigations designed to prevent inadvertent contamination of otherwise BSE-free tissues.

III.B.3.b.1. *Relevant anatomy of bovine small intestine*

The small intestine of cattle attaches at its most proximal end (closest to the mouth) to the most distal (closest to the anus) chamber of the ruminant stomach. This most proximal segment of the small intestine is the duodenum. Distal to the duodenum is the very long jejunum. According to the North American Natural Casings Association, the duodenum and jejunum are used for natural beef casings (NANCA 2004). Distal to the jejunum is the ileum, which is estimated to be two to three feet long (NANCA 2004). The distal-most portion of the ileum, or “distal ileum,” is estimated to be 12 to 18 inches long. It attaches to the most proximal portion of the large intestine, the cecum, at what is termed the “ileocecal junction” or “ileocecal orifice.” Just distal to the ileocecal junction is the cecocolic junction.

III.B.3.b.2. *Mitigations to exclude distal ileum from imported small intestine*

Since the distal ileum is the only portion of the small intestine demonstrated to contain BSE infectivity, its exclusion would remove any associated infectivity from the rest of the small intestine. In this section, we discuss the mitigations required to adequately remove the distal ileum.

USDA Food Safety Inspection Service (FSIS) and HHS Food and Drug Administration (FDA) have determined that the distal ileum can be effectively removed from the rest of the small intestine. They have also determined that the remaining small intestine can be used as human food if the distal ileum is removed (FSIS 2005, FDA 2005). To ensure the complete removal of the distal ileum, both FSIS and FDA require the removal of at least 80 inches of the uncoiled and trimmed small intestine as measured from the cecocolic junction (FSIS 2005, FDA 2005). Their regulations also allow for the facility to submit an equivalent process to the respective agency for approval. Based on the description of bovine intestinal anatomy, above, we concur that removal of this tissue will exclude the distal ileum.

An authorized veterinary official of the Government of Canada will be required to certify that any product containing bovine small intestine does not include distal ileum as defined above. This certification will ensure that conditions in Canada meet the standards that USDA considers appropriate for safe trade in this commodity.

III.B.3.c. Conclusions: Infectivity release via importation of bovine intestines

The studies described above demonstrate that the distal ileum, but not the remainder of the bovine intestine, is a potential source of BSE infectivity. The distal ileum is the only portion of the bovine intestine for which OIE recommends any trade restrictions because of BSE (OIE 2006a). Similarly, both the Food and Drug Administration (FDA 2005) and the FSIS (FSIS 2005) have concluded that if the distal ileum is removed from the small intestine of cattle, the remainder of the small intestine can be used for human food.

Because bovine intestinal tissue, excluding the distal ileum, has not been shown to contain infectious levels of the BSE agent, even if derived from infected cattle, and because the distal ileum can be removed at slaughter in a manner to avoid contamination, APHIS concludes that it is highly unlikely that any BSE infectivity would be released into the United States via bovine intestines imported from Canada.

III.C. Projections and composition of cattle imports from Canada under the proposed rule

Projections of cattle imports from Canada under the proposed rule, prepared by USDA's Economic Research Service (ERS), are based on forecasts of Canada's annual cattle inventories multiplied by the share of inventory expected to be imported by the United States. ERS has forecasted the percentage of cattle that would be imported, by purpose (immediate slaughter, feeding for slaughter, and breeding), and gender, based for the

most part on data from 1992 through May 2003. The cattle categories and import percentages, shown in Table 4, are discussed here briefly.

Table 4. Projected percentages of cattle imports from Canada with the proposed rule		
	<u>Percentages</u>	
	<u>Sub-group</u>	<u>Overall</u>
Slaughter cattle		82
Steers/heifers*	53.2	
Cows	21.1	
Bulls and stags	3.9	
Calves*	3.7	
Stockers/feeders*		13.8
Breeding cattle		4.2
Dairy heifers/cows*	3.6	
Beef heifers/cows*	0.4	
Bulls*	0.2	
Total		100

*As described in the following paragraphs, most of the animals in these categories would be less than 2 years of age at the time of import.

III.C.1. Slaughter Cattle

Slaughter cattle, which would comprise up to 82 percent of the cattle imported, are slaughtered almost immediately after crossing the border. They are expected to have a somewhat older age distribution for the first year that the rule would be in effect (we assume for this analysis that this will occur in 2007), with most of the surplus inventory eliminated by year end.

Slaughter cattle can be categorized into 1) steers¹⁰ and heifers¹¹; 2) cows, bulls and stags¹²; and 3) calves¹³ (ERS 2004; Purdue 2006). Steers and heifers are the largest category, and would comprise about 53 percent of imports. In both the United States and Canada, slaughter steers and heifers are generally on feed from 120 days to more than 200 days before slaughter. Most of them are between 16 and 24 months of age at slaughter, with some over 26 months. Because more females than males are kept in the population for breeding (Matthews and Short 2001), we expect approximately 60 percent of this sub-group of slaughter cattle to be steers and 40 percent to be heifers.

Historically, the percentage of steers has ranged from 53 to 65 percent, depending on the level of heifer retention for the Canadian breeding herd.

¹⁰ Steers are bovine males castrated prior to sexual maturity.

¹¹ Heifers are bovine females that have not yet given birth.

¹² Stags are male bovines castrated at or near maturity.

¹³ Calves are young male or female bovine animals under one year of age.

Slaughter cows are expected to comprise roughly 21 percent of imports. Approximately 60 percent of these would be dairy cows. Their median age would be approximately 3.8 years, with most between 3 and 6 years of age. Slaughter beef cows would average 6 years of age, with most between 5 and 7 years of age.

Slaughter bulls and stags are past breeding service and would comprise less than 4 percent of imports. Most are 5 to 7 years of age, with a median age of approximately 5.5 years.

Vealers and light calves would also comprise less than 4 percent of imports. They include cattle from less than 1 month old up to 8 months, with most between 4 and 5 months of age.

III.C.2. Feeders/stockers

Weaned steers and heifers (about 9 months of age) and yearlings (mostly 12 to 15 months of age) imported for feeding constitute the second largest group after slaughter cattle, about 14 percent of the overall total. This category is also the most variable, having ranged from 3 percent to 46 percent of Canadian cattle imports. The wide range is due to varying weather/forage conditions, feed costs, and inventory changes reflecting the cattle cycle. These cattle are all destined for feedlot finishing and slaughter, but may be placed on pasture for several months of gain before feedlot placement. They are generally placed on feed for 120 to over 200 days before being slaughtered.

III.C.3. Breeding cattle

Breeding animals would comprise approximately 4 percent of imports. They are destined for dairy and beef breeding herds and would be eventually culled like their U.S. herd mates. Dairy heifers and cows constitute the largest share of breeding cattle. They are mostly bred (pregnant) heifers that are 15 to 19 months of age and due to calve. They enter the milking herd at about 24 to 26 months of age. Young, open (not pregnant) dairy heifers and a small number of cows that have calved complete this category.

Beef heifers and cows would comprise less than 1 percent of imports and, like the dairy breeding stock, would include open and bred heifers and cows.

Bulls for breeding would constitute a very small proportion of total imports. This category includes beef bulls 15 to 24 months of age, as well as a few dairy bulls.

ERS has estimated the total projected number of animals to be imported for 2007 (the year in which we anticipate implementing the rule) through 2026 to provide twenty years of input data to be incorporated into the exposure model informing the exposure assessment below. These total annual projections are broken out into the various use categories in Table 5 below.

Table 5. Projected imports of various cattle use types for years 2007 through 2026.

CASE: shares based on sum of annual imports over 1992-2003														
Projected cattle imports to US from Canada, by category -- 1,000 head														
	Canadian			U.S.	SLAUGHTER CATTLE						BREEDING CATTLE			Stocker/
	Inventory	Pct	Pct		Steers &	Cows	Bulls	Vealers /	Sub-	Dairy cows	Beef cows	Bulls	Sub-	feeders
YEAR	,000 hd.	change	exported	,000 hd.	heifers		& stags	Light calves	total	/ heifers	/ heifers		total	(male+fem)
2007	14,400	97.1	9.5	1,368	728	289	54	51	1,121	50	5	3	58	189
2008	14,050	97.6	9.0	1,265	673	267	50	47	1,036	46	5	3	53	175
2009	14,250	101.4	8.5	1,211	644	255	48	45	993	44	4	3	51	167
2010	14,300	100.4	9.0	1,287	685	271	50	48	1,055	47	5	3	54	178
2011	14,375	100.5	9.0	1,294	688	273	51	49	1,060	47	5	3	54	179
2012	14,450	100.5	9.0	1,301	692	274	51	49	1,066	47	5	3	55	180
2013	14,550	100.7	9.0	1,310	697	276	51	49	1,073	47	5	3	55	181
2014	14,650	100.7	9.0	1,319	701	278	52	49	1,081	48	5	3	55	182
2015	14,250	97.3	9.5	1,354	720	286	53	51	1,110	49	5	3	57	187
2016	14,100	98.9	9.5	1,340	713	283	53	50	1,098	49	5	3	56	185
2017	14,425	102.3	9.0	1,298	691	274	51	49	1,064	47	5	3	55	179
2018	14,500	100.5	9.0	1,305	694	275	51	49	1,070	47	5	3	55	180
2019	14,650	101.0	9.0	1,319	701	278	52	49	1,081	48	5	3	55	182
2020	14,875	101.5	9.0	1,339	712	282	53	50	1,097	49	5	3	56	185
2021	15,200	102.2	9.0	1,368	728	289	54	51	1,121	50	5	3	58	189
2022	15,350	101.0	8.5	1,305	694	275	51	49	1,069	47	5	3	55	180
2023	15,450	100.7	8.5	1,313	699	277	52	49	1,076	48	5	3	55	182
2024	15,650	101.3	8.0	1,252	666	264	49	47	1,026	45	4	3	53	173
2025	16,000	102.2	8.0	1,280	681	270	50	48	1,049	46	5	3	54	177
2026	16,000	100.0	8.5	1,360	724	287	53	51	1,115	49	5	3	57	188

Source: Expert opinion, USDA Economic Research Service, Market and Trade Economics Division, Animal Products, Grains, and Oil Seeds Branch. Based on "USDA Agricultural Baseline Projections to 2015," United States Department of Agriculture, Interagency Agricultural Projections Committee, Baseline Report OCE-2006-1, February 2006, http://www.usda.gov/occe/commodity/ag_baseline.htm; and import data 1992-2003; and projected Canadian inventory.

III.C. 4. Projected bison imports

Table 6. Projected Bison Imports

Projected Bison Imports to United States from Canada by Usage Category				
YEAR	Canadian Bison Exports to United States	Slaughter	Breeding	Stocker/Feeders
2007	4,000	2,500	250	1250
2008	3,150	2,400	250	500
2009-2026	2,500	2,000	250	250

Source: ERS Market and Trade Economics Division, Animal Products Branch.

Based on Department of Commerce, Bureau of the Census import data from 1996-2002, the ERS Market and Trade Economics Division, Animal Products Branch estimated the composition of projected bison imports. Because of restrictions on the movement of bison from Canada into the United States, they anticipate a higher number of exports in 2007 and 2008 than for subsequent years. From 2009, approximately 2500 bison are projected to be imported per year, with the following breakdown across three usage types. The numbers per usage type per year are presented in Table 6 and the overall breakdowns are described below:

Slaughter Bison

The primary share of the imports, 80 percent, is likely to be for immediate slaughter. About 80 percent of these imports are male, 5 percent female and about 15 percent unknown.

Breeding Bison

Of the 2500 bison expected to be imported per year, approximately 10 percent are for breeding purposes. Roughly 70 percent of these animals are female and 30 percent male. These imports provide a source of genetic diversity to the U.S. bison herd.

Feeder Bison

Feeders comprise about 10 percent of imports, of which roughly 90 to 95 percent are male.

III.D. *Release conclusions*

In the preceding sections of the release assessment, we have presented several pieces of evidence that together indicate that, even when making risk-inflating assumptions, very little BSE infectivity is expected to be released into the United States via the proposed additional commodities imported from Canada. In this final portion of the release assessment, we integrate the findings of these various sections.

III.D.1. Likelihood of BSE release via import of live bovines

In section III.A., we present results of a modified, previously published model (BSurvE) that estimates the BSE prevalence in Canada's standing (August 2006) cattle population. Because of uncertainty in various parameters and constraints of the model itself, it incorporates some important simplifying assumptions that over-estimate the prevalence values. For example, the positive test result from the case of Canadian origin that was diagnosed in the United States was included among the positive surveillance results (numerator), whereas negative and clinically normal animals of Canadian origin exported to the United States were not included in the population total (denominator). This admittedly biased approach inflates the Canadian prevalence estimates.

We assess the likelihood of release of BSE infectivity over an extended period of time, assuming that the proposed rule would apply into the foreseeable future. In order to allow sufficient time for several potential amplification cycles (roughly 5-7 years each), we have evaluated release over a 20 year period: 2007-2026. We considered different scenarios for release, providing both qualitative and quantitative inputs to inform the exposure assessment.

In section III.B.1, we discuss the proposed mitigation of limiting animals intended for import to those born after the date the feed ban was effectively enforced. The evidence presented about the feed ban and related activities in Canada support the conclusion that cattle born in Canada on or after March 1, 1999, will have a very low risk that they have been exposed to the BSE agent. This conclusion contributes to the qualitative inputs evaluated in the exposure assessment. As further described below, however, data limitations prevent quantitative consideration of this mitigation.

As noted previously, our prevalence estimates are for the standing cattle population in August 2006. As described in Section III.A., implementation of a ruminant feed ban results in decreasing BSE prevalence over time (DEFRA 2006, EC 2005a; Cohen, et al. 2001; 2003; Cohen and Gray 2005). The methods we use to estimate prevalence, however, cannot project the changes expected over the 20-year period of our analysis. Therefore, we infer that the BSE prevalence and subsequent release of infectivity from Canada for each of the 20 years after the anticipated implementation of the proposed rule (estimated as 2007) are less than expressed by our quantitative estimate. We use these prevalence estimates in the exposure assessment in two different ways. First, we use them to provide a current estimate of possible release via live animal imports in the first year of our analysis, and then we qualitatively consider the most likely scenario of decreasing prevalence over subsequent years. Second, as we allow for less likely outcomes, we use these prevalence estimates as risk-inflating numeric surrogates for the release input parameter of the exposure model (Attachment 2) used to inform our exposure assessment.

Using the methods described in Section III.A., we have two estimates of expected (mean) prevalence in the Canadian herd for August 2006. One estimate (BSurvE), based on the accumulated Canadian BSE surveillance data, expresses the expected prevalence as

3.9×10^{-6} infected cattle. When combined with import projections for 2007 from Table 5 in Section III.C., this estimate predicts that less than 6 of the over 1.3 million imported animals will be infected (Table 7). This value is higher than that for nearly all other years in the analysis because, as seen in Table 5, 2007 is a year in which a relatively large number of animals is projected to be imported. Therefore, the values for 2007 reflect the highest number of “expected” infected animals.

The other estimate (BBC) of the August 2006 BSE prevalence in Canada incorporates both prior surveillance data and evidence from the UK on the impact of a feed ban. Given that Canada has an effective feed ban, as described in Section III.B.1., this estimate is likely the more realistic. Moreover, since imported live bovines from Canada must be born after the date of effective implementation of the feed ban, this lower estimate (expected value= 6.8×10^{-7}) is far more applicable to the current proposal. Using this approach, as indicated in Table 7, we “expect” roughly 0.94 infected animals in that year. Once again, this prediction is for 2007, a year in which our import projections predict higher volumes, and therefore compared to the subsequent 19 years, represents the highest number for this prevalence estimate.

Furthermore, the two prevalence estimates are calculated for the total cattle population in Canada, including cattle born before the date which APHIS concludes that the feed ban was effectively enforced. Because of data limitations, we did not calculate the prevalence by birth cohorts. Epidemiological evidence in the UK suggests that cohorts born after effective implementation of the feed ban are much less likely to develop disease than cohorts born before the effective implementation of such a ban (DEFRA 2006). Therefore, Canadian cattle born after the date the feed ban was effectively enforced are much less likely to be exposed to infective material and become infected with BSE. This evidence is considered in the qualitative evaluation of the most likely scenario in which prevalence in Canada decreases over the next 20 years. However, this evidence is not considered in the less likely scenarios represented in the quantitative analysis. In those scenarios, we assume that all animals are equally likely to have been exposed to infective material and that the prevalence remains constant over the next 20 years.

As noted in the import projections, the majority of imports are expected to be less than two years of age at the time of import. Therefore, in 2007, this large group of younger animals would be born many years after both the initial implementation of the feed ban, and the date at which we consider the ban to have been effectively enforced. In subsequent years, these animals would be born an increasingly longer time after those dates. Therefore, they would be even less likely to have been exposed to infected feed. Like the evidence described in the preceding paragraph, this information is considered in the qualitative evaluations, but not in the quantitative evaluations.

Table 7 below presents projected percentages, total (number) and infected cattle imports by usage type from Canada for 2007, based on estimates of August 2006 prevalence. These values are presented not as estimates of predicted release, but to reasonably inform the quantitative exposure simulations in Section IV of this document.

Table 7. Projected percentages, total (number), and infected cattle imports by usage type from Canada for 2007. The two prevalence estimates reflect the two methods used in Section III.A.

	<u>Percentages</u>		<u>Number imported 2007</u>	<u>Number infected 2007</u>	
	<u>Sub-group</u>	<u>Overall</u>		<u>Prevalence=</u>	<u>Prevalence=</u>
				<u>6.8*10⁻⁷</u>	<u>3.9*10⁻⁶</u>
Slaughter cattle		82	1,121,000	0.76	4.37
Steers/heifers	53.2		728,000	0.50	2.84
Cows	21.1		289,000	0.20	1.13
Bulls and stags	3.9		54,000	0.04	0.21
Calves	3.7		51,000	0.03	0.20
Stockers/feeders		13.8	196,000	0.13	0.76
Breeding cattle		4.2	60,000	0.04	0.23
Dairy heifers/cows	3.6		51,000	0.03	0.20
Beef heifers/cows	0.4		5,000	0.00	0.02
Bulls	0.2		3,000	0.00	0.01
Total	100	100		0.94	5.37

III.D.1.a. *Release of BSE infectivity via import of live bison*

Although the bulk of the live bovines expected to enter the United States following implementation of the proposed rule would be cattle, we also expect the entry of some bison. These animals will also be required to be born after the date of the effective feed ban. As reported in Section III.C., except for the first two years, we expect approximately 2,500 bison to enter annually. In the absence of evidence to the contrary, we assume that the prevalence of BSE in bison is the same as that in cattle. Since no cases have been reported in North American bison, this assumption likely overestimates the risk associated with importation of this species. Nonetheless, even when assuming that bison are as likely as cattle to be infected with BSE, and when using August 2006 BSE prevalence estimates, we would expect only 0.0098 infected bison imported annually, or one in 103 years, when not considering the additional evidence of the expected impact of a feed ban, currently, or in the future. Even for 2007, the year in which the greatest number of bison exports is expected (4000), we calculate only 0.0156 infected bison to be imported.

Given that the feed ban applies to all ruminants, including bison, we expect that it has reduced the prevalence in that population as much as it has in cattle. When incorporating the additional evidence from the UK on the expected impact of a feed ban into the August 2006 prevalence estimate, and assuming 2500 animals imported per year, the “expected” number of infected bison drops to 0.0017 per year, or one in 588 years, even when assuming no subsequent drop in prevalence over that period. Given the

essentially negligible rate at which we might, even with cautious assumptions, introduce BSE infectivity via bison, we have elected not to analyze this pathway further.

III.D.2. Release of BSE infectivity via import of blood and blood products

As demonstrated in Sections III.A. and III.B.2., multiple steps in the risk pathway act as safeguards against the release of BSE infectivity from Canada into the United States via imported blood and blood products. First, as described in Section III.A., the underlying BSE prevalence in Canada is now extremely low (less than 7 per 10 million cattle under the BBC model, or less than 4 per million under BSurvE Prevalence B), and is expected to decrease further. Therefore, the chance of collecting blood from an infected animal is very small. Even if one of the very few infected animals were a source of imported blood or blood products, several steps, or nodes, in the risk pathway act to further diminish the likelihood of release. The first of these is the evidence that, even in infected animals, BSE infectivity has not been detected in the blood of cattle. Furthermore, the most commonly imported blood-derived commodity, fetal bovine serum, passes through two additional risk-reducing nodes: the very low likelihood of maternal transmission and, once again, the evidence that BSE does not localize to bovine (in this case, fetal) blood.

Additional nodes that apply to both adult- and fetal-derived blood reflect the continued drop in likelihood attributable to blood fractionation. Specifically, even in those species in which any TSE infectivity has been found in whole blood, it is typically at a much lower level in the plasma or serum from which the vast majority of blood-derived commodities are derived. Therefore, even if bovines were to have some infectivity in their blood, it would not persist in the significantly traded commodities (e.g., FBS and BSA).

The pathways described in the previous paragraphs reflect a series of sequential, and hence, multiplicative nodes. The likelihood of infectivity being released directly (not secondary to cross-contamination) via imported blood and blood products is the conceptual product of the likelihoods of each node contained within the pathway. Thus, the product of each of these very low likelihoods reflects essentially negligible risk.

III.D.2.a. *Likelihood of cross-contamination at slaughter*

The possibility of cross-contamination at slaughter of bovine blood with infectivity from high risk tissues is an additional potential risk pathway that must be considered. Because this pathway is separate, in part, from the one described above, its effects are additive. Cross-contamination could potentially occur if, during slaughter or processing, collected blood were contaminated with specified risk materials (SRMs). Like the pathway described in the preceding paragraph, the cross-contamination pathway would also be greatly reduced by the very low prevalence of BSE in Canada. However, the cross-contamination risk pathway could bypass the sequential safeguards described above. Existing prohibitions on compressed air stunning will prevent the creation of brain tissue emboli that could potentially contaminate the blood (CFIA 2006a). In order to further minimize the likelihood of release associated with this pathway, we are proposing

mitigations that will effectively prevent cross-contamination during the collection process. Specifically, the slaughtered animal (in some cases, the dam of the animal from which the fetal blood is collected) must pass antemortem inspection, the uterus must be removed intact and taken to a separate area, and blood (both fetal and non-fetal) must be collected in a closed system.

Based on the evidence and the proposed mitigations described in this document, we conclude that there is a negligible likelihood of additional BSE infectivity being introduced into the United States via blood and blood products imported from Canada.

III.D.3. Release of BSE infectivity via import of small intestines other than distal ileum

As for the two groups of commodities described above, live animals and blood and blood products, the likelihood of release of infectivity via imported small intestine from Canada is reduced in large part by the very low BSE prevalence demonstrated in Section III.A. Based on the discussions in Sections III.A. and in the introduction to this release summary, we conclude that the current prevalence in Canada will decrease further. If, despite this presumably decreasing prevalence, an infected animal were slaughtered, two additional risk pathway nodes further reduce the likelihood of BSE release via the import of bovine small intestine other than the distal ileum.

The first of these nodes is the likelihood that BSE infectivity would be present in the small intestine, other than the distal ileum. Section III.B.3. presents abundant evidence that such a likelihood is exceedingly small. In essence, all research indicates that when BSE is localized to the small intestine, it is detected only in the distal ileum. All other portions are considered to be free of infectious levels of the agent.

The second node, in parallel, and thus additive in nature to the first, addresses the exclusion of the potentially infectious distal ileum. In Section II.B.3., we discuss the mitigations which require the removal of this SRM. FSIS and FDA have determined that the distal ileum can be effectively removed by discarding the most distal 80 inches of the uncoiled and trimmed small intestine. Their conclusions are supported by anatomic evidence that the bovine ileum is only two to three feet long (NANCA 2004). Moreover, FDA and FSIS both conclude that small intestine from which the distal ileum has been so removed can be used for human consumption. An authorized veterinary official of the government of Canada will be required to certify that any product containing bovine small intestine adheres to these requirements.

Therefore, the two crucial nodes in the potential risk pathway associated with importation of small intestine other than distal ileum that reduce the likelihood of infectivity are the absence of infectivity in these tissues, and mitigations to ensure adequate removal of potentially infective distal ileum. Based on the presented evidence, we conclude that the likelihood of introducing BSE infectivity in bovine small intestine other than distal ileum imported from Canada is negligible.

III.D.4. Release conclusions

In summary, based on the evidence and proposed mitigations discussed in the release assessment, we conclude that the likelihood of releasing BSE into the United States from Canada via importation of live bovines, blood and blood products or intestines is extremely low. The numeric estimates presented above are used as inputs for the exposure model discussed in the next section of the document, and do not in themselves represent our expectation of release.

IV. Exposure Assessment

IV. A. *Live Bovines*

This section of the risk assessment evaluates the pathways by which infected Canadian cattle, if imported, might expose U.S. cattle to BSE, and the likelihood that these pathways might lead to the establishment of the disease in the U.S. cattle population. The nature and likelihood of these pathways depend in large part on mitigations acting in series and in parallel which reduce the likelihood that BSE will be established in the United States.

As demonstrated in the release assessment, we conclude that the prevalence of BSE among Canadian cattle is extremely low. The models which we used to evaluate prevalence produce two estimates of prevalence for August 2006: one that does not include additional evidence from the UK on the expected impact of a feed ban (BSurvE Prevalance B), and one that does (BBC). We maintain that the latter estimate is more appropriate for this risk assessment because the proposed mitigation requiring that all imported live bovines are born on or after March 1, 1999, means that these animals are subject to the implemented feed ban. In order to determine the significance of this assertion, we include the higher prevalence estimate in the sensitivity analysis discussed below.

As described in Section III.A.2.a of the Release assessment, empirical observation and simulation studies document a continued drop in prevalence following implementation of a feed ban. Because the rate at which this drop may occur in Canada cannot be adequately quantified, we assume for the purposes of performing a quantitative analysis that prevalence (and thus the likelihood of release) will remain constant over the 20 years of the analysis (2007-2026). Therefore, the numeric outputs presented in this section reflect this highly cautious assumption. Our interpretation of these results, however, is further informed by evidence that the prevalence will decrease over this time period.

IV.A.1. Pathway Analysis: Barriers to BSE transmission and amplification

If an infected animal were to be imported, then each of the remaining barriers outlined here reduces the level of infectivity in the system. For an infected imported Canadian animal to transmit infection to a U.S. cow, four sets of barriers must be crossed:

1. Slaughter controls and dead animal disposal
2. Rendering inactivation
3. Feed manufacturing and use controls
4. Biologic limitations to susceptibility

Current FSIS slaughter restrictions in the United States decrease the likelihood that any infectious raw materials from an infected imported animal will be incorporated into the human or animal food supply. These restrictions include antemortem inspections, which reduce the amount of infectivity that could pass into the rendering process. BSE-infected cattle in the end-stages of infection, and containing the greatest amount of infectivity, will typically present with central nervous system signs or as downer cattle and will be condemned. Prohibiting the slaughter of downer cattle and those otherwise displaying clinical signs recognized as consistent with BSE infection, explicitly eliminates the potential for their infectivity reaching humans. Such a condemnation will also trigger a diagnostic investigation of the suspect animal, including a test for BSE. If positive, its infectivity will be inactivated by incineration. Also, without slaughter as an option for handling downer cattle, some farmers and ranchers may dispose of such cattle on their premises, thereby eliminating these cattle as a source of infectivity in cattle feed.

The FDA's 1997 ruminant feed ban, found in Title 21 of the *Code of Federal Regulations* Part 589.2000 (FDA 2006) regulates rendering, feed manufacture and use of prohibited feeds to reduce the risk of BSE recycling in the United States. Rendering processes in the United States will inactivate significant levels of the agent, further reducing the level of infectivity in prohibited bovine MBM. These processes inactivate much of any potentially remaining infectivity by subjecting the material to intense heat and pressure. Furthermore, federal regulations require that bovine material sent to a rendering facility must be kept separately from low risk material and must be correctly labeled for use by feed processors. These requirements reduce the likelihood of cross-contamination and mislabeling by renderers.

If a fraction of the hypothetical BSE infectivity were to escape destruction at the rendering facility, it would need to by-pass controls imposed to prevent cross-contamination and ensure proper labeling of rendered materials (at the renderer) and feeds produced using prohibited MBM (at the feed mill). The controls preventing cross-contamination and mislabeling act in parallel to one another and are additive in their risk reduction effects. Proper separation of infectivity by prevention of cross-contamination and mislabeling, act in series with risk reduction steps occurring up to and including rendering. Therefore, controls preventing cross-contamination and mislabeling are multiplicative with these earlier steps in their risk-reduction effects.

The likelihood of exposure to any infectivity remaining in properly manufactured and labeled, but prohibited feed, is reduced by the ban on misfeeding of these feeds to ruminants. However, even if some remaining infectivity were fed to cattle, in order for disease transmission to occur, an individual animal must consume a dose high enough to be infectious given that animal's age-specific susceptibility distribution. In other words, the amount of infectivity present must be adequate to infect an animal ingesting that feed.

If the dose is too low, exposure will likely not result in infection. Epidemiological and simulation studies indicate that animals are most susceptible before 4 months of age (Wilesmith, et al. 1988; 1992; 1992a; Ferguson, et al. 1997; De Koeijer, et al. 2004).

Moreover, in the extremely unlikely event that an animal should become infected from contaminated feed, it is unlikely that infectious levels of the agent from that animal would be transmitted to other cattle because infectivity from that animal must also circumvent all of the barriers discussed.

IV.A.2. Quantitative evaluation of BSE exposure and spread in the United States

APHIS has arranged for the primary author of the Harvard BSE model to simulate the impact of the mitigations described above on the likelihood of exposure, establishment and spread of the BSE agent in the United States following the release of infectivity in live animals imported from Canada (see Attachment 2). Therefore, the current BSE simulation model is a revision of one developed jointly at Tuskegee University and at the Harvard Center for Risk Analysis (Cohen, et al. 2001; 2003).

Simulation description modified from Cohen, et al. 2003

The simulation model can be thought of as consisting of four components. The first component characterizes the lifecycle of cattle in the US, quantifies the potential infection of animals at different points during this cycle, and characterizes their ultimate disposition (slaughter, death due to natural causes followed by either disposal or rendering, and death due to BSE infection followed by either disposal or rendering). The second component of the model describes how animals sent to slaughter are processed. Tissue may be disposed of, sent to rendering, or prepared for potential human consumption. The third component of the model characterizes the disposition of material sent to rendering. That material may exit the system (*e.g.*, because it will be disposed of, exported, or used to produce feed for animals other than cattle) or end up in feed that is administered to cattle. In this way, the model keeps track of the extent to which BSE might spread to additional cattle in the U.S., expressed both in terms of additional BSE-infected cattle, and in terms of the disease's reproductive rate, R_0 . This information is the focus of the APHIS analysis. The final component of the model quantifies infectivity in material presented for human consumption.

IV.A.2.a. *Methodology*

Historically, the Harvard BSE model (Cohen, et al. 2001; 2003) has been used to evaluate the impact of various alternatives scenarios and risk management options on the possible spread of BSE within the U.S. cattle herd and the potential for human exposure to the BSE agent. The model simulates what might happen if BSE were introduced into the U.S. cattle population. In doing so, the model estimates whether BSE would develop into a self-sustaining epidemic if it were introduced into the United States, or if its prevalence

would tend to decrease over time, leading eventually to its eradication. Our use of the model focuses on the dynamics of the disease in cattle, rather than possible human exposure.

The probability that BSE could be perpetuated in the U.S. cattle population depends on the average number of new cases of disease that result from each existing case. This value, designated R_0 , is referred to as the epidemic's basic reproduction rate (Anderson 1991). If R_0 exceeds unity (one), the disease will tend to spread. Conversely, if R_0 is less than unity, the number of cases will tend to decline over time, and ultimately the disease will die out.

Previous versions and updates reflecting new domestic regulations include parameters likely to influence the predicted spread of the disease. Briefly, these input parameters address:

- Dynamics of U.S. cattle population
- BSE related mitigations during slaughter, rendering and feed production and usage
- The degree of compliance with restrictions on animal slaughter, rendering and feed practices
- The amount of infectivity being carried by an infected animal in different tissues at different times of the incubation period
- Inherent characteristics of cattle, such as age-related susceptibility

IV.A.2.a.1. Current (2006) updates to the BSE Exposure Model and input parameters

In order to evaluate the effects of importing cattle born on or after March 1, 1999 from Canada and to incorporate newly available evidence, the author has modified the model in the following ways:

- Cohen, et al. (2001; 2003) evaluated a single importation of infected cattle introduced at the beginning of the simulation. The current revision allows for repeated importations of infected cattle and specification of the age at import, sex, animal type (dairy, beef slaughter, or reproductive beef), age at infection, and expected slaughter age.
- Explicit modeling of potential cattle exposure to the BSE agent via administration of poultry litter in cattle feed. The simulation model incorporates the proportion of prohibited MBM used in poultry feed (separate values are specified for dead and healthy slaughter cattle), and the proportion of poultry litter that is administered intentionally as cattle feed (Attachment 2, Section 2.1.8).

The current version of the model also incorporates updated parameter estimates:

- Efficacy of SRM removal at slaughter
- Proportion of animals that are rendered
- Mislabeling and cross-contamination at rendering
- Mislabeling and cross-contamination at feed mills

- Disposition of MBM
- Pessimistic value of misfeeding for sensitivity analysis

These parameters are described in the following sections along with parameter updates employed in Cohen and Gray 2005, and other significant, although unchanged parameters. In order to be consistent with its historic use in the Harvard model and in Attachment 2, we use the term “pessimistic values” in this context to refer to the plausible higher values used in the sensitivity analysis.

IV.A.2.a.2. *Significant and/or updated (2005-2006) parameters*

The following discussion enumerates and provides the rationale for changes in the input parameters most relevant to our analysis. These changes are consistent with new BSE mitigations, compliance data, and new data on key parameters known to influence the spread of the disease. They include relevant changes made in a recent update of the model performed for USDA FSIS (Cohen and Gray 2005), and new changes implemented specifically to inform the current risk assessment.

In addition to revisions in the model and its parameters, we also discuss the most important nodes in the risk pathway. Other nodes that have not been deemed to be epidemiologically important (such as maternal transmission or the feeding of plate waste or tallow to cattle) are addressed in earlier publications (Cohen, et al. 2001; 2003) and are not revisited here.

IV.A.2.a.2.(a) Import of infected cattle

As described in the release assessment, the numeric representations of the number of infected cattle introduced into the United States are based on (1) August 2006 estimates of the BSE prevalence in Canada (Section III.A. and Attachment 1), and (2) the number of cattle we expect to import over the 20 years of the analysis (Section III.C.). Table 7 (Section III.D.) shows the estimates for the number of infected animals imported by age, sex, and type for the first year in which the proposed rule may be implemented, 2007.

The most likely assumption, which we have not attempted to quantify, is that the prevalence will continuously decrease from the current estimate over the 20-year analysis period. In this assumption, the possible numbers of infected animals imported is highest in the first year in which the proposed rule may be implemented, and subsequently decreases. This assumption does not provide numeric estimates of the importation of infected animals necessary for simulation in the exposure model. Therefore, the exposure model and its results by necessity include the less likely assumption that Canadian BSE prevalence remains constant through 2026.

Based on these numeric representations of BSE release from Canada, the attached, updated exposure model evaluates the outcome of the introduction of infectivity assuming BSE prevalence in Canada is 6.8×10^{-7} . This estimate incorporates the UK data on the effect of a feed ban.

Although the release section produces two numeric estimates of BSE prevalence in Canada, the proposed mitigation requiring that all imported live bovines are born on or after March 1, 1999 means that these animals are subject to the feed ban. We therefore focus our discussion of the impacts of the proposed live animal imports on results predicted when assuming that Canada's feed ban has reduced BSE prevalence as effectively as that observed in the UK. We evaluate the impact of relaxing this assumption in the sensitivity analysis, in which we analyze the model's outputs assuming the higher prevalence value (3.9×10^{-6}) which omits the additional UK evidence.

Once infected animals are introduced into the system, the model evaluates how mitigations during slaughter, rendering, and feed production reduce the amount of infectivity potentially available to be recycled and fed to bovines.

IV.A.2.a.2.(b) Slaughter process

BSE infected animals showing clinical signs of disease are at the end of the incubation period and therefore carry a high infectivity load (Wells, et al. 1996; 1998). Therefore, identification of high risk animals, including those displaying clinical sign of BSE infection at ante-mortem inspection, reduces the probability that these animals and the large amount of infectivity they may carry will enter the normal slaughtering process. As part of the ante-mortem inspection, FSIS veterinarians routinely condemn animals showing clinical signs of systemic disease, non-ambulatory status and/or exhibiting clinical signs compatible with BSE, including central nervous system impairment. For standard surveillance, a condemnation of an animal exhibiting clinical signs of BSE triggers a diagnostic investigation of the suspect animal, including a test for BSE. If positive the animal is destroyed mainly by incineration.

The scenarios simulated in the attached exposure model (Attachment 2) reflect current mitigation measures related to the disposition of non-ambulatory animals and track the ambulatory status of cattle infected with BSE. Antemortem inspection and ambulatory status probabilities are based on Cohen and Gray 2005.

In the event that infected animals pass the ante-mortem inspection, many tissues not used for human consumption, including tonsils and distal ileum of all animals and nervous tissue-derived SRMs of animal over 30 months old, go to rendering. As in earlier versions of the model, the author cites FSIS' statement that SRMs are effectively removed 99 percent of the time (FSIS 2005).

IV.A.2.a.2.(c) Proportion of animals that are rendered

Sick, non-ambulatory and dead animals can either be rendered or disposed of in other ways (e.g., burial on farm and landfill disposal). Disposal other than rendering prevents potential infectivity in non-rendered animals from inadvertently entering cattle feed.

Dead stock that is not disposed of on the farm, animals condemned on antemortem inspection at slaughter and non-ambulatory cattle from all types of cattle operations are typically collected by rendering firms. Eastern Research Group, Inc. (ERG 2005) and Informa Economics (Informa 2004) prepared detailed estimates of farm mortalities and materials rendered. Informa (2004) estimates that approximately 35 percent of cattle found dead on farm and downers in the United States are rendered (41.9 percent rendered by volume). In contrast, ERG (2005) using other industry-supplied data estimated that the number of cattle mortalities and downers rendered is 17 percent.

In response to comments on its initial analysis and in recognition of the uncertainty about this parameter, FDA substituted new industry data into the analysis, revising its estimate from 17 to 33 percent with an upper bound of 42 percent (FDA 2005a, page 58588). The current analysis (Attachment 2) assumes the higher value of 42 percent to reflect those cattle dying on farm that are rendered. This parameter value is lower, however, than the 85 percent assumed in previous analyses (Cohen, et al. 2001; 2003).

IV.A.2.a.2.(d) Rendering process

Although rendering of infected bovines can potentially allow BSE infectivity to pass into ruminant feed, several mitigations diminish its likelihood of doing so. FDA's 1997 feed ban (FDA 2006) requires that renderers must (1) keep specific records on the manufacture of rendering products, (2) have processes in place to prevent commingling of ruminant and non-ruminant MBM, and (3) ensure that materials containing prohibited MBM are labeled conspicuously with the statement, "Do not feed to cattle and other ruminants." Furthermore, as discussed below, rendering itself serves as an effective mitigation against the perpetuation of infectivity.

IV.A.2.a.2.(d)i. Inactivation during rendering

Although rendering practices vary among plants, the Harvard model (Cohen, et al. 2001; 2003; Cohen and Gray 2005) cite evidence from industry sources, estimating that 95 percent of ruminant MBM is produced using processes that result in at least one log reduction in BSE infectivity. Specifically, 5 percent of ruminant MBM is rendered using a batch system that reduces infectivity by 3.1 logs; 45 percent of MBM is rendered using a continuous flow system to which fat is added that reduces infectivity by 2 logs; and 45 percent of MBM is rendered using a continuous flow system without fat added that reduces infectivity by 1 log. Only 5 percent of MBM is rendered using a vacuum system that results in no reduction in BSE infectivity. The infectivity reduction by type of rendering system is based on inactivation studies (Taylor, et al. 1995; 1997).

We used this evidence to calculate the expected (average) reduction in infectivity from rendering to be 1.4 logs. Thus, roughly 96 percent ($1-10^{-1.4}$) of BSE infectivity is destroyed during rendering allowing only 4 percent of BSE infectivity to survive the rendering process.

IV.A.2.a.2.(d)ii. Cross-contamination and mislabeling at rendering

The likelihood of cross-contamination and mislabeling at rendering depends in large part on the potential presence of risk materials in the facility. Cohen, et al. (2001; 2003) assume that nearly 50 percent of raw material from ruminants is delivered to rendering plants that process only prohibited material, eliminating the possibility of cross-contamination at the renderer (although mislabeling is still possible). Citing industry sources, the authors also assumed that approximately 5 percent of such high risk material is delivered to rendering plants that process both prohibited and non-prohibited material (so-called mixed rendering plants). In these facilities, both cross-contamination and mislabeling are possible. We assume that no mislabeling or cross-contamination occur at dedicated “non-prohibited” rendering facilities.

In order to estimate mislabeling and contamination probabilities, we rely on data collected by FDA/CVM¹⁴ prior to September 2003. Compared to more recently collected inspection data, these data better detail the nature of the violations discovered, reporting the total number of firms with at least one violation and designating each violation as a case in which: 1) products were not labeled as required, 2) the facility did not have adequate systems to prevent co-mingling, or 3) the facility did not adequately follow record keeping regulations. More recent data report violations only in terms of the type of action indicated – *i.e.*, Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI)¹⁵.

As described in Cohen and Gray 2005, these compliance data indicate that mislabeling was detected in 2.3 percent of inspected renderers and possible commingling (cross-contamination) was detected in 1.8 percent of inspected renderers. The model uses these values to indicate the relative likelihoods of these nodes within the risk pathway. Both of these values reflect decreases from higher estimates based on older compliance data used in earlier versions of the Harvard BSE exposure model. Additional details on these parameter values are in the attached exposure model document (Attachment 2). We note here, however, that the use of these data is likely to produce compliance estimates that are lower than current levels because compliance rates with the FDA regulation improved

¹⁴ Compliance program implementation details can be found at http://www.fda.gov/cvm/CVM_Updates/BSE0806.htm.

¹⁵ From the FDA CVM Web site (http://www.fda.gov/cvm/CVM_Updates/BSE0806.htm): According to FDA, “An OAI inspection classification occurs when significant objectionable conditions or practices were found and regulatory sanctions are warranted in order to address the establishment’s lack of compliance with the regulation. An example of an OAI inspection classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented.”

“A VAI inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the Ruminant Feed Ban. These include provisions such as minor recordkeeping.

since 2002. For example, the FDA/CVM update of June 2005 (FDA CVM 2005) indicates that 2 (1.1 percent) out of 176 rendering firms handling prohibited materials were classified as OAI.

IV.A.2.a.2.(e) Disposition of meat and bone meal

The revised BSE exposure model includes updates on the disposition of rendered materials. In previous versions, the authors estimated that 15 to 30 percent of MBM produced in the United States was exported. This percentage dropped substantially in 2004 to 5 percent of production (NRA 2005). In addition, because the current model explicitly addresses the poultry litter pathway, the proportion of MBM destined for poultry feed needed to be specified. To incorporate both of these changes to the model, we assume that 50 percent of prohibited MBM goes to feed mills producing prohibited feeds (excluding poultry feed); 5 percent of prohibited MBM goes to mixed feed mills and the remaining 40 percent goes to poultry feed mills. In addition to the poultry litter pathway, ruminant MBM from both dedicated prohibited material renderers and mixed rendering plants that may contain infectivity may be incorporated into ruminant feed if it is mislabeled at the feed mill as non-prohibited feed.

The updated BSE exposure model (Cohen and Gray 2005; Attachment 2) also adjusts for increases in the proportion of exported non-prohibited MBM to 30 percent (NRA 2005). This proportion and those going to other feed mill types are presented in Table 8, along with the respective parameter values used in earlier versions of the model.

Table 8. Differences in the parameter regarding the disposition of MBM used for the Cohen, et al. 2001/2003* and 2005/2006 Risk Assessments

	Prohibited Renderer		Non-Prohibited Renderer		Mixed Renderer	
	P	NP	P	NP	P	NP
P Feed Producer (other than poultry feed)	50% (63%)	50% (63%)	NA ^(a)	50% (0%)	50% (63%)	50% (0%)
NP Feed Producer	0% (0)	10% (0)	NA ^(a)	10% (85%)	0% (0%)	10% (85%)
Mixed Feed Producer	5% (5%)	10% (5%)	NA ^(a)	10% (5%)	5% (5%)	10% (5%)
Poultry Feed Producer	40% (NA) ^(b)	0% (NA) ^(b)	NA ^(a)	0% (NA) ^(b)	40% (NA) ^(b)	0% (NA) ^(b)
Out (Unavailable to U.S. Cattle)	15% (32%)	30% (32%)	NA ^(a)	30% (10%)	5% (32%)	30% (10%)

*Values for the Cohen, et al. 2001/2003 risk assessments are in parenthesis

Abbreviations: P – prohibited, NP – non-prohibited, NA – not applicable

(a) We assume no product from a non-prohibited renderer is labeled as prohibited

(b) Poultry feed producer was not modeled in the 2001/2003 Risk Assessments

IV.A.2.a.2.(f) Feed manufacturing process

The FDA's ruminant feed regulations (21 CFR 589.2000) (FDA 2006) prohibit the inclusion of high risk source materials in ruminant food. However, some prohibited MBM might cross-contaminate non-prohibited feed, or prohibited feed may be mislabeled as non-prohibited. Information on mislabeling and contamination during the feed manufacturing process used in Attachment 2 is based on 2002 FDA feed ban compliance data (FDA 2002). These data report that 4 percent of prohibited feed is mislabeled, and 1.9 percent of prohibited feed cross-contaminates non-prohibited feed. These values replace higher, less certain estimates used in earlier versions of the model. Table 2 in Attachment 2 shows the differences in the parameter values associated with the handling of prohibited materials during the feed manufacturing process used for the Cohen, et al. 2001/2003 and the 2006 risk assessments.

Although lower than previous estimates, the values used are still higher than suggested by more recent compliance data. Such data show that from a total of 9,575 inspections of feed mills conducted during the fiscal year 2004 and the first half of the fiscal year 2005, 165 firms (1.7 percent) were identified as firms handling animal feeds containing prohibited mammalian protein that were not meeting the labeling requirements. In addition, of the 9,575 inspections of feed mills, 41 (0.4 percent) of the inspections identified cross contamination or commingling problems in firms that handle animal feeds containing prohibited mammalian proteins (FDA 2005a). Therefore, as for the rendering data above, we conclude that our higher 2002 estimates over-estimate the amount of cross-contamination and mislabeling that currently occurs in feed mills.

IV.A.2.a.2.(g) On-farm misfeeding

We recognize that even if all of the above safeguards are 100 percent effective in preventing contamination of ruminant feed with potentially infective prohibited material, cattle may be exposed to such materials via misfeeding on the farm. This pathway is in parallel to and therefore additive with those prohibiting cross-contamination and mislabeling of rendered material and feed. However, like cross-contamination and mislabeling, the potential impact of, and mitigations from the prohibition on misfeeding are in series, and hence multiplicative with all of the risk reduction steps occurring up through rendering.

The base case scenario for Cohen, et al. (2001; 2003) assumes that 1.6 percent of correctly labeled prohibited feed is misfed to cattle, with a pessimistic estimate of 30 percent used in the sensitivity analyses. Since the sensitivity analyses have shown that this parameter is very influential, (Cohen, et al. 2001; 2003), the National Grain and Feed Association and the American Feed Industry Association provided new data for the estimates (NGFA and AFIA 2005). Their data indicate that while the original expected value of 1.6 percent is reasonable, the pessimistic value used in the sensitivity analyses should be reduced to 5 percent.

IV.A.2.a.2.(h) Poultry litter exposure pathway

As described in the section on disposition of MBM, current FDA regulations allow the use of ruminant MBM (prohibited MBM) in poultry feed. In the United States, poultry litter can be legally used as a feedstuff for ruminants. Because poultry feed may contain ruminant meat and bone meal which is prohibited in ruminant feed, there is a potential risk that poultry litter may contain spilled poultry feed or potentially intact infectivity excreted in fecal waste. Cattle fed the poultry litter may then be exposed to infected materials. The current assessment incorporates this potential pathway into the larger evaluation of the risk of the importation of infected Canadian cattle. Like misfeeding, the poultry litter pathway is additive to the controls implemented to prevent cross-contamination and mislabeling, and is multiplicative to the controls up to and including rendering.

Poultry litter is a waste by-product of poultry production, containing bedding material, fecal matter, feathers and spilled poultry feed. It is generally only used as cattle feed in particular geographic areas in major broiler producing states where cattle and poultry production enterprises are in close proximity. Since the exposure model simulates the fate of infectivity in the entire U.S. herd, we use information provided by relevant industry representation (Custer personal communication 2005), estimating that on average, 1 percent of poultry litter nationwide will be used in cattle feed.

We assume that prohibited ruminant protein (and any infectivity which it may contain) is most likely to enter poultry litter via spilled poultry feed. We are uncertain, however, of the proportion of infectivity that enters the litter. We therefore over-estimate this proportion by assuming that 100 percent of any infectivity that may be in poultry feed goes to the litter.

IV.A.2.a.3. *Sensitivity analysis*

The exposure model includes a sensitivity analysis to identify potentially important assumptions. These assumptions were evaluated by holding all but one set of assumptions equal to their base case values. The set of assumptions were set to pessimistic values to see if doing so influences key model predictions – in particular, for this analysis, the predicted number of cattle infected with BSE in the United States over a 20 year period. In addition to determining if the parameters impact the outputs, the sensitivity analysis also provides a ranking of the parameters with respect to the relative magnitude of their effects.

The parameters analyzed include four “endogenous” factors inherent to the U.S. system that influence the fate of introduced infectivity, and one “exogenous” factor, external to the system, that influences the amount of infectivity introduced. The endogenous parameters assessed in the sensitivity analysis are:

- (1) Mislabeling and contamination – We have revised the base case values for these parameters to take into account new data on compliance rates. The sensitivity

analysis evaluates the impact of these revisions by using the previous base case values from Cohen, et al.'s 2003 report as the pessimistic values in the current analysis. In particular, for the sensitivity analysis we increase the mislabeling rates to 5 percent for both MBM and feed production. We increase contamination rates to 14 percent for MBM production, and 16 percent for feed production (Attachment 2 Section 2.2.4).

(2) Misfeeding – The base case value for this parameter is 1.6 percent. We investigate the impact of using the pessimistic value of 5 percent for this parameter (Attachment 2 Section 2.2.9).

(3) The render reduction factor – We change the distribution of render reduction factors using the worst case assumptions for this parameter from Cohen et al.'s October 2003 report.

(4) The proportion of poultry litter used in cattle feed - The base case value for this parameter is 1 percent. The sensitivity analysis investigates use of 5 percent for this parameter.

The exogenous parameter assessed in the sensitivity analysis is:

(5) Importation of infected animals as a function of Canadian prevalence estimate – Using the BSurvE method described in Section III.A. we can assess the impact of imports from Canada assuming a higher Canadian BSE prevalence estimate. In particular, omitting the additional information on the impact of the UK feed ban from the calculation provides a BSE prevalence estimate for Canada of approximately 3.9×10^{-6} , nearly six times higher than the base case prevalence (6.8×10^{-7}) which includes the assumption of the impact of a feed ban.

In the final sensitivity analysis scenario, all six uncertain parameters were simultaneously set to their pessimistic levels. Doing so allows us to explore the impact of this unlikely, but possible situation.

IV.A.2.b. *Results*

IV.A.2.b.1. *Base Case Results*

The following paragraphs summarize the results from the model simulations. As previously noted, the most likely prevalence assumption – the prevalence decreases continuously – was not included in these simulations. Therefore, the base case as described reflects the less likely assumption that the prevalence stays the same for the period of this analysis.

Under base case conditions, our results indicate that the expected number of infected cattle occurring in the United States over 20 years as a result of importing cattle from Canada is 21 animals. Most of these infected animals (90 percent) would be imported directly, while the remaining 10 percent (approximately 2 animals) would represent secondary infections (i.e., native U.S. cases). Of the 21 in the United States, 0.67 animals

would survive to show clinical signs (Attachment 2, Appendix 2A). The expected (average) value of the reproductive constant for BSE (R_0) is far less than 1 (0.04), indicating no possibility of establishment of BSE in the United States as a result of the introduction of potential infectivity from Canada.

We are 95 percent confident that at base case levels, the total number of infected animals in the United States over 20 years of the analysis will not exceed 30 animals. We are also 95 percent confident that there will be 24 or fewer animals imported and six or fewer native U.S. cases (Attachment 2, Appendix 2A). In addition, we are 95 percent confident that under base case assumptions, R_0 will not exceed 0.25.

IV.A.2.b.2. Sensitivity Analysis Results

The sensitivity analysis indicates that, of the endogenous parameters, the most important sources of uncertainty are the misfeeding rate and the extent to which poultry litter is used in cattle feed (Attachment 2).

The exogenous source of uncertainty, the prevalence estimate with its resulting release of infected animals, is the most important source of uncertainty. The higher value used in the sensitivity analysis is 5.7 times greater than that used in the base case. Not surprisingly, the number of imported infected animals (108) and the number of new cases (12) are 5.7 times greater than those expected in the base case. The R_0 value of 0.075 is only slightly higher than that at the base case (0.04), reflecting that the U.S. system is essentially unchanged by additional introduced infectivity.

When using pessimistic values for all five uncertain parameters analyzed, the average number of total infected cattle (including imports) over the 20 years of the analysis is 150. Of these, 42 are U.S. born animals and less than 8 survive long enough to develop clinical signs. Furthermore, in this highly unlikely scenario, the reproductive constant, R_0 , remains consistently less than 1, with an expected value of 0.23 (Attachment 2, Appendix 2A). That is, even under the worst set of assumptions considered here, BSE infectivity introduced via live animals from Canada will not establish, and will instead disappear from the population.

IV.A.3. Live Animal Qualitative Exposure Assessment

As discussed in the release section (Section III.D.), evidence indicates that implementation of a ruminant feed ban results in decreasing BSE prevalence over time. Therefore, in the most likely scenario, prevalence will decrease in Canada over the next 20 years. In addition, the proposed mitigation (imported animals must be born on or after March 1, 1999) would ensure that imported animals are less likely to have been exposed to the BSE agent. Finally, based on ERS projections, the majority of imports are expected to be less than two years of age at the time of import. For example, approximately 75 percent of animals imported in 2007 would have been born in 2005 or later (Table 4). As the 20-year time frame for the analysis proceeds, these animals would be born an increasingly longer time after the feed ban was effectively enforced.

However, without a quantitative estimate for the precise rate at which Canada's BSE prevalence may fall, we cannot produce numeric values that accurately represent this scenario.

In addition, the import projections indicate that a higher number of imports would be expected in 2007, the first year that the proposed rule could be implemented. When this projection is combined with the BBC prevalence estimate – determined to be more applicable to the current proposal – less than one infected animal would be expected to be imported that year. With the expectation that the prevalence would decrease, and the mitigative effects of both the import requirements and the young age of animals at the time of import, the highest likelihood of release would be in 2007. Qualitatively, we would therefore expect that prevalence, release, and hence, the number of infected animals occurring in the United States as a result of exposure, would be lower than any of the results of the quantitative model.

IV.A.4. Live Animal Exposure Summary

In summary, if infectivity at the levels analyzed, either quantitatively or qualitatively, were introduced into the United States from Canada, biological factors (e.g., age-dependent susceptibility), and mitigations reducing the likelihood of transmission at slaughter, rendering and feed manufacturing and use, prevent BSE amplification in the United States. Furthermore, the quantitative model produces estimates of the reproductive constant, R_0 , that predict that any imported infectivity will ultimately disappear from the population.

IV.B. *Qualitative exposure assessment for blood and blood products imported from Canada*

In the release assessment, we presented evidence that bovine blood and blood products from Canada are highly unlikely to carry BSE infectivity into the United States. According to the OIE's risk assessment guidelines (OIE 2006b), if the likelihood of release is determined to be negligible, the assessment may be concluded. However, in order to maintain consistency in our approach across the three commodities considered, we have elected to assess the exposure and consequences associated with all the commodities, even if their likelihood of release is negligible. Therefore, in this section, we assess the likelihood of exposure to infectivity if, despite the evidence, such commodities were indeed contaminated with the BSE agent. Because the primary blood products imported into the United States for use in manufacture of veterinary biologics and drugs are fetal bovine serum (FBS) and bovine serum albumin (BSA), we focus our analysis on the potential exposure pathways associated with those products.

The pathways under consideration are those which might allow potential BSE infectivity in imported FBS and BSA to persist through the steps in the manufacture of animal biologics and pharmaceuticals, and result in cattle exposure to, and subsequent infection with BSE. As explained in Section III.B.2, we utilize TSE studies on other species because no comparable work can be done on BSE in cattle blood, given that it has never been detected.

IV.B.1. Risk mitigation by processing of FBS and other blood products

Extrapolating from studies in other species, we expect that some of the processing steps used in preparation of FBS and BSA and the products derived from them further reduce the likelihood of BSE transmission. Those steps which may result in mitigation of BSE risk by removal through separation techniques, potential inactivation through gamma irradiation, and dilution, are discussed here.

Several reasons have been given for the marked decrease in TSE infectivity during these separation processes. The pathogenic conformation of the prion protein (PrP^{Sc}) has a low solubility in aqueous solution, forms aggregates readily, and has an affinity for adhering to surfaces (Foster 1999). These attributes contribute to the reduction of the likelihood of BSE transmission via FBS and BSA through centrifugation and filtration (Foster 2004), processes which are used in the preparation of FBS and plasma fractions and in the collection of cell culture products for use as biologics or in the manufacture of pharmaceuticals.

Plasma, serum and other derivatives are obtained from various processes applied to whole blood. Serum is derived from whole blood through the following process. Whole blood is collected into sterile blood bags and is allowed to clot. The clotted blood is centrifuged for removal of the clot and separation of serum from the blood cells. This initial separation step has been demonstrated to remove TSE infectivity from other species' serum fraction (Brown, et al. 1999; Houston, et al. 2000; Hunter, et al. 2002; Brown, et al. 1998). The resulting serum may include nutrient proteins, growth factors, hormones, lipids, minerals, and metabolites necessary for cell culture. The serum is decanted, prefiltered, pooled with a variable number of other animals' serum, sterile filtered, and frozen. Because of the properties described in the preceding paragraph, the decanting and filtration steps would further remove any infectivity that might possibly have remained in the serum. Furthermore, the pooling step would dilute any single donation from a subclinical case of BSE.

Pooled FBS is subjected to filtration using 0.1-0.2 micron filters and, for cell culture applications, irradiated to mitigate the likelihood of potential contamination by bacterial and viral agents. According to APHIS Center for Veterinary Biologics records, gamma irradiation is applied commercially at c. 25-50 kiloGray (2.5-5 megaRad) prior to its use in vaccine production. Most commercially applied mitigations are appropriate for prevention of bacterial and viral disease transmission via blood-derived biologics. TSE infectivity, however, is in general highly resistant to conventional inactivation techniques (Taylor 2003).

Unlike heating and other standard steps to ensure freedom from microbial contaminants, gamma irradiation may reduce BSE infectivity. Miekka, et al. 2003 demonstrated that scrapie was inactivated by an estimated 1.5 log₁₀ in human albumin 25 percent solution, using 50 kGy, while causing only moderate alterations to the albumin. We do not, however, have direct evidence for the efficacy of gamma irradiation as a BSE mitigation

in bovine blood products. Thus, although we may speculate that slightly lower levels of gamma irradiation used to prevent the transmission of viruses in commercially processed bovine sera may have some mitigative effects on levels of BSE infectivity, we have no direct evidence of such.

To prepare plasma products from whole blood, anticoagulants such as sodium citrate or EDTA are added to the collection receptacle to prevent clotting. This blood, collected generally from live adult bovines, is then centrifuged and filtered. Using fractionation techniques such as cryoprecipitation, centrifugation and filtration, plasma is commercially separated into various components, among which are Fraction II containing immunoglobulins and Fraction V containing albumin (BSA) (Comer 2004, p. II.23). In experimental rodent models, several studies have shown that the very low level of plasma infectivity is dramatically reduced during this fractionation process (Brown 2001). It has been observed that discarding of Fraction III and Fraction IV from immunoglobulin and from albumin, respectively, results in further TSE removal for various strains (scrapie, BSE, CJD) in rodent models (Foster 2004). Separation is achieved by removal of the precipitate. The supernatant and sometimes a redissolved precipitate are then commonly clarified by further filtration. Because of the BSE agent's properties described above, these additional separation steps would further reduce the likelihood of BSE transmission. The overall process reduction factors for TSE infectivity of the various plasma proteins have been estimated to be quite large. For example, the infectivity reduction factor is 10^{13} for albumin and 10^9 for immunoglobulins (Foster 1999).

Although whole blood or buffy coat transfusion has resulted in experimental transmission of BSE or scrapie between sheep (Hunter, et al. 2002), and in iatrogenic transmission of vCJD between persons in the UK (Farshid, et al. 2005), transmission by other blood products has not been demonstrated in natural animal hosts of TSEs nor in natural infection of animals or humans (Brown 2001). No transmissions of vCJD have been attributed to plasma derivatives, even among such groups as hemophiliacs that must often use these products (Taylor 2003; WHO 2003). We infer that these observations may result from the reduction in TSE infectivity due to the fractionation processes used in the preparation of these products.

IV.B.2. FBS and blood product use in veterinary vaccine and drug manufacture

FBS is used as a nutrient in cell culture growth media during production of viral vaccines and to propagate difficult-to-grow microorganisms. The basic steps for production of veterinary vaccines are equivalent to those used in the production of human vaccines (FDA 2001). Both often require FBS and sometimes BSA, used as growth media or as stabilizers in a number of biological products, supporting bacterial growth and cell cultures that propagate virus.

The cell lines used in vaccine production are not permissive for prion replication (Harris 1999; Solassol, et al. 2003), so there is no opportunity for amplification of possible TSE contamination. The vaccine virus is grown and harvested from the cell culture, and

largely separated from the cell supernatant containing the FBS. There may be trace amounts of FBS remaining in the viral pellet, but this represents a minute amount of the final vaccine dose. Thus, even if BSE-infected FBS were used in bovine vaccine production, the FBS itself does not remain in the final product in amounts adequate to result in infection.

The evidence presented here demonstrates the sequential barriers to exposure to BSE infectivity from blood and blood products imported from Canada:

1. prion protein has a low aqueous solubility, readily forms aggregates and adheres to surfaces, reducing the likelihood of it persisting through the various separation and filtration steps throughout the FBS and vaccine manufacture process;
2. blood products such as BSA pass fractionation steps that further reduce the likelihood of BSE being transmitted;
3. the additional steps in the manufacture of vaccines and other products serve to separate potential infectivity from the processed product.

This evidence is further supported by the absence of an epidemiologic link between vaccine administration and clinical cases of BSE in cattle (WHO 2003). Therefore, we conclude that even if BSE were present in bovine blood products collected in Canada, the likelihood of exposure of animals in the United States to such infectivity is negligible.

IV.C. Qualitative analysis for exposure resulting from the importation of small intestine other than the distal ileum

In the preceding release assessment, we demonstrate that the likelihood for the introduction of BSE infectivity in imported bovine intestine from Canada is extremely low. In this section, we evaluate the pathways by which BSE infectivity could potentially expose U.S. cattle, if despite our earlier findings it were released in imported bovine small intestine other than the distal ileum. We also assess the likelihood that these pathways might lead to exposure that could potentially cause animal disease and the establishment of BSE in the U.S. cattle population.

As described in Section IV.A., the feeding to ruminants of ruminant protein is expressly prohibited by FDA (21 CFR 589.2000, FDA 2006). This feed ban applies to both non-edible intestine, as well as that intended for human consumption. Therefore, exposure of cattle to BSE infectivity assumes subsequent misdirection, mislabeling, misfeeding, or cross-contamination in feed processing. As demonstrated in the quantitative exposure assessment for imported live bovines, spread via these various pathways is extremely rare, even when considering importation of entire animals. We infer, therefore, that imported Canadian bovine intestine is highly unlikely to be fed to U.S. cattle, or lead to spread of BSE.

We recognize that some small fraction of imported inspected and prepared for human consumption may be legally offered per FDA's "plate waste" exemption¹⁶. However,

¹⁶ 21 CFR 589.2000 exempts the feeding of "inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste...)"

very few firms are processing human waste food for ruminant consumption (Pritchett 2004 personal communication). Furthermore, since FDA requires that the plate waste be further heat processed for feed, it may be subject to rendering processes that can inactivate the agent, further reducing the level of infectivity in MBM (Cohen, et al. 2001; 2003).

Given the above evidence, we conclude that exposure of U.S. cattle to BSE in bovine small intestine imported from Canada is extremely unlikely. Therefore, the likelihood of infection and subsequent establishment of the disease in the U.S. cattle population is negligible.

V. Consequence Assessment

In accordance with OIE's guidelines, the first two sections of this animal import risk assessment examine the *likelihood* of BSE release and exposure. The consequence assessment is intended to address the *impacts* expected if, despite the likelihood of release and exposure estimated in the preceding sections, new cases of BSE were to occur in the United States. Consequences requiring consideration are economic and environmental. To fulfill obligations under the National Environmental Policy Act (NEPA), impacts to the human environment are addressed in the accompanying environmental assessment. The following discussion addresses the economic impacts that we would expect if additional BSE cases were to result from the proposed regulatory change. Following OIE's guidelines, we subsequently combine the impacts described in the consequence assessment with the likelihoods described in the release and exposure assessments to evaluate the overall risk in the risk estimation section.

The economic impact of BSE includes a variety of costs; some are long-term costs that continue regardless of new cases, others are one-time costs associated with new cases. One long-term impact is the potential loss from actions taken by foreign governments to restrict imports of U.S. live bovines, beef and beef products. These tend to decline over time as exporting and importing countries find ways to resume mutually beneficial trade while maintaining the safety of the beef supply. International organizations such as OIE have developed international science-based standards to permit safe international trade in beef from countries that have BSE. U.S. producers incur other long-term costs by complying with domestic regulations to protect animal and human health. U.S. producers and processors must comply with a variety of regulations designed to prevent the BSE agent from entering the ruminant feed chain and to prevent potentially infected ruminant tissues from entering the human food chain. U.S. regulations pertaining to SRM removal, restrictions on use of SRMs, and other changes mandated of the beef processing and feed processing sectors are examples of this type of impact. Another long-term cost is that for BSE surveillance which will continue into the foreseeable future.

The impacts of any new cases of BSE are confined to the incremental costs associated with those actual cases. These potential impacts are of two types, regulatory costs and domestic market impacts from consumer reaction to additional BSE cases. Based on the U.S. experience with native BSE cases detected, the regulatory costs per case total

approximately \$250,000 for epidemiological investigations and indemnity costs for animals sacrificed as part of those investigations.

The potential domestic market impacts from any new BSE cases are difficult to predict, in part because they may depend on how many new cases are found in a particular time period (Coffey, et al. 2005). The results of a mail survey of approximately 2,500 persons in 2004 showed significant differences in consumers' responses depending on how many hypothetical new BSE cases were reported (Coffey, et al. 2005). Other surveys performed in 2004 (Coffey, et al. 2005) all reported that between 15-20 percent of consumers indicated they would reduce beef consumption if a BSE case were found.

This expressed or stated preference about consuming beef after BSE cases must be interpreted in light of the U.S. consumers' actual or revealed preference as shown by their actions. After the first BSE case was found in the United States in 2003, the annual increase in demand for beef in 2004 was the highest since 1980 (Kansas State University, AgManager Info 2006). According to the same source, demand in 2005 dropped slightly from 2004 levels, but still exceeded every other year since 1991. Thus, what American consumers have done in response to a BSE case occurring is quite different from what was predicted by survey results. Repeated consumer polls have revealed only a small minority of the population is concerned about the possibility of being exposed to BSE from U.S. beef and over 90 percent of the population believes the U.S. beef supply is safe from BSE (NCBA 2005). Based on this evidence, we find little reason to expect that additional cases of BSE would have any significant impact on U.S. beef consumption.

The impact of additional BSE cases on U.S. export markets will probably also be minimal. After the first U.S. BSE case was discovered, many of the 114 nations which imported U.S. beef banned our beef and live animals, but over half – including our largest export market, Japan - have resumed importing U.S. beef (USDA 2006)¹⁷. The joint U.S.-Japan press statement for resuming trade in beef and beef products after market closures in response to finding BSE in the United States contained a provision noting “additional BSE cases will not result in market closures and disruption of beef trade patterns without scientific foundations” (USDA 2004).

Thus, we recognize that ongoing costs of BSE prevention will continue even in the absence of future cases. The costs that we may expect to be associated with the investigation of potential future cases are relatively minor. Finally, we do not foresee significant costs due to drops in domestic beef consumption or imposition of additional trade barriers to international export markets.

VI. Risk Estimation

The BSE risk associated with the proposed additional imports of bovine commodities from Minimal Risk Regions (currently, Canada) is the conceptual product of the likelihood of release, the likelihood of exposure and the resulting economic

¹⁷ The temporary closure of the U.S. export market to Japan on 20 January 2006 was a response to a specific commodity concern and not to the likelihood of BSE infection in the U.S. herd.

consequences. Potential impacts to the human environment are addressed in the accompanying environmental assessment.

As in the exposure and release assessments, we estimate the risks associated with each of the proposed commodity groups separately. We then combine these respective risks to estimate the cumulative BSE risk of importing the proposed commodities.

VI.A. *Live bovines*

Release is unlikely because prevalence is low and mitigation requiring imported animals to be born on or after March 1, 1999 would significantly decrease the likelihood that those animals had been exposed to infectivity. We expect the prevalence to decrease continuously over the next several years. With this effect, any possibility of release, already low, decreases each year with the decreasing prevalence (until the disease is eradicated). Although this scenario is the most likely, the Bayesian Birth Cohort (BBC) approach as described is surveillance-based and cannot incorporate empirical and simulated evidence to project expected decreases in prevalence levels over time. Therefore, our expectation that prevalence in Canada, and hence release of BSE infectivity will decrease over time, cannot be incorporated into the quantitative model which informs our exposure assessment. Based on the evidence presented in this document, APHIS concludes that the likelihood of BSE release from imported Canadian cattle born on or after March 1, 1999 is extremely low.

Import of bison is allowed in the proposed rule, but would constitute such a small fraction of imports (approximately 0.2 percent), that they are not analyzed separately. We assume that our conclusion of an extremely low likelihood of release for cattle also applies to bison.

Even though APHIS concludes that decreasing Canadian prevalence is most likely, we quantitatively analyze the impact of the constant BSE prevalence produced by the BBC model to simulate potential BSE exposure in U.S. cattle. This calculation provides a reasonable upper bound on our estimate of prevalence and subsequent release of infectivity, which we refer to as “cautious.” Using this cautious value, the model estimates release of approximately 19 infected bovines over the 20 years of the analysis. As an expression of our uncertainty regarding the application to Canada’s prevalence calculation of the additional UK data on the efficacy of a feed ban, we performed a sensitivity analysis which excluded this additional information. That even more cautious, and less likely, scenario results in the importation 108 infected bovines over 20 years.

Qualitatively, the exposure assessment demonstrated that, because we expect Canada’s prevalence to decrease over time, and because of the barriers to BSE transmission in the United States, that the likelihood of BSE exposure and establishment in the U.S. cattle population is negligible. Quantitatively, the exposure assessment evaluated the impact of the numbers of infected animals imported using our assumption of constant prevalence, on the likelihood of U.S. cattle exposure to BSE. We based our evaluation on the Harvard Center for Risk Analysis BSE simulation by Cohen et al. (2001, 2003), updated

to incorporate new evidence and domestic regulations and the proposed changes considered here. This model indicates that even with assumptions that over-estimate the possible level of infectivity released into the United States, there is little spread of disease to U.S. animals. The release of approximately 19 imported infected animals, leads to approximately two U.S. cases as secondary spread and 0.67 animals showing clinical signs over the 20 years of the analysis.

The reproductive constant for BSE (R_0) is far less than the value of 1.0 necessary to maintain disease in the U.S. cattle population. Even when higher plausible values were applied for all uncertain parameters evaluated in the sensitivity analysis, R_0 is 0.23, well below 1.0 (Attachment 2, Appendix 2A).

The significance of this R_0 value is magnified by the expectation, despite the assumptions in our models, that BSE infectivity in Canada (and thus released into the United States) is likely to decrease over time. Thus, although the results of the BSurvE model assume no change in prevalence over time, empirical evidence (DEFRA 2006, EC 2005a) and simulation studies (Cohen, et al. 2001; 2003) suggest that Canada's feed ban will continue to decrease BSE prevalence in that country. Thus, we expect the number of native cases to be less than those predicted in our analysis.

Considering evidence provided in the consequence assessment (Section V.), we expect that the 0.67 clinical cases that we estimate may occur over 20 years (equivalent to 1 in 30 years) will result in negligible economic costs of BSE. Although clinical cases are the only manifestation of BSE in an animal population, APHIS acknowledges that the possibility of preclinically infected animals is a concern. Thus, although human health is not the focus of this assessment, we note that, even our quantitative model, which includes multiple sources of risk over-estimation, indicates that over the 20 years of the analysis, only 45 cattle oral infectious dose-50 (ID_{50}) units will potentially be available for human exposure. Although this result is discussed in more detail in the accompanying environmental assessment (APHIS 2006), we note here that compared to estimated potential exposure levels in the UK of 54 million cattle oral ID_{50} units over 24 years (Comer and Huntly 2003), this number is insignificant.

VI.B. Blood and blood products

In the release assessment we concluded from presented evidence that multiple steps in the risk pathway act as safeguards to prevent release of BSE infectivity from Canada via imported blood and blood products. First, the BSE prevalence in Canada is extremely low. Therefore, the likelihood of collecting blood from an infected animal is small. Even if an infected animal were a source of imported blood or blood products, several steps, or nodes in the risk pathway act to further diminish the likelihood of release. The first is that, even in infected bovines, BSE infectivity has not been detected in blood. Second, the likelihood of cross-contamination at collection is significantly reduced by the proposed mitigations. We conclude that the likelihood of release of BSE infectivity in bovine blood and blood products is negligible.

In the exposure assessment, we further examine the role of various separation and processing steps in reducing infectivity. We also note the absence of an epidemiological link between administration of vaccines manufactured using tissue culture supported by fetal bovine serum and clinical cases of BSE (WHO 2003). We conclude that the steps in the production and use of products manufactured with bovine blood or its derivatives are likely to further reduce any possible infectivity.

Given both the negligible release of BSE and exposure of bovines to any such introduced infectivity via the importation of bovine blood and blood products from Canada, we conclude that extremely few or no U.S. cases of BSE would result. Therefore, the consequences and resulting risk of their importation are negligible.

VI.C. Bovine small intestine other than the distal ileum

In the release assessment we present evidence that the small intestine of BSE infected cattle has detectable infectivity only in the distal ileum. Other portions of the small intestine that have been examined do not contain detectable infectivity. We also supply evidence that FSIS' and FDA's regulations ensure adequate removal of the distal ileum, thus effectively mitigating the likelihood of contamination of exported bovine intestines with infectivity from the distal ileum.

In the exposure assessment, we examine possible pathways for bovine exposure to infectivity that may potentially be released from Canada in bovine small intestines other than the distal ileum. We found no epidemiologically significant exposure pathways. Combining these findings, we conclude that the joint likelihood of BSE release and subsequent exposure of bovines to infectivity from imported bovine intestines other than the distal ileum is negligible. We further conclude that this negligible likelihood would result in extremely few or no U.S. cases of BSE. Therefore, the consequences and resulting risk of the importation of these commodities are negligible.

VI.D. Conclusion of Risk Estimation for all commodity groups considered

We conclude that over the 20 years of the analysis, BSE will not become established in the United States and that very few, if any, U.S. born animals will be infected. Release of infectivity into the US via any of the commodities described is unlikely, as outlined in the qualitative discussions. However, even if release of some infectivity occurred via imported live animals – as in the less likely scenarios modeled quantitatively – there is minimal if any spread to native US animals and the disease does not become established. Economic costs secondary to BSE introduction via the importation of these commodities will therefore be negligible.

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