Response to peer review of risk assessment of Bovine Spongiform Encephalopathy (BSE) risks associated with the importation of certain commodities from BSE minimal risk regions (Canada)

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September 2007

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Following Office of Management and Budget (OMB) guidance (OMB 2004), the risk assessment published with the proposed rule for revision of the commodities allowed entry under the bovine spongiform encephalopathy (BSE) minimal risk regions regulations (APHIS 2006) was submitted for peer review. The analysis was reviewed by four internationally known experts in the fields of BSE, modeling, quantitative risk assessment and its application to regulatory decision making, and international health standards. Each reviewer addressed specific issues raised in the peer review charge. In particular, the reviewers were asked if: the analysis was scientifically sound, transparent, and consistent with international standards (e.g., those by the World Organization for Animal Health (OIE)); the application of external assessments or models was appropriate; and the assumptions were justified and reasonable. The charge to the reviewers, the original and revised risk assessments, and the peer review report are available at http://www.aphis.usda.gov/peer_review/peer_review_agenda.shtml.

As stated in the executive summary of the peer review report (RTI 2007, pp.ES-1 to ES-2):

> All reviewers agree with the risk assessment conclusion that the risk of establishment of BSE in the U.S. cattle population is negligible. All reviewers noted that the several assumptions in the risk assessment actually represent worst case scenarios, so the overall finding that the BSE risk is negligible is reasonable. All reviewers also agreed that the risk assessment followed the international standards and guidelines by the World Organization for Animal Health (Office International des Epizooties [OIE]). Furthermore, the reviewers were impressed with the scientific rigor of the assessment in terms of using existing literature and models appropriately and making sound assumptions. They also commended the presentation and organization of the report.

The reviewers were supportive of the methods, evidence, and conclusions presented by the Animal and Plant Health Inspection Service (APHIS) in the risk assessment. They also asked a variety of questions and suggested minor refinements. We made changes to the risk assessment in response to editorial suggestions, without noting them individually here. In this document, we respond to the content-related questions asked by the reviewers. We have organized the comments raised by individual reviewers and our responses according to the order of the section of the risk assessment to which they most apply. We intend for this approach to facilitate the reader's concurrent referral to resulting changes made in the revised risk assessment. Finally, we indicate in each case whether we have amended the risk assessment in response to the comment.

Introduction

Issue: One reviewer suggested that we include the criteria for a country to be listed as a minimal risk region (RTI 2007, p. 6-3).

Response: We have included the criteria for a BSE minimal risk country as defined in regulations in Title 9 of the Code of Federal Regulations (9CFR), Part 94.0, in the revised Risk Assessment.

Issue: A reviewer suggested that we more explicitly list the specific risks to be addressed in the assessment (RTI 2007, pp. 6-2 to 6-3).

Response: The risk of BSE evaluated in the assessment is the expected impact of importing from Canada live animals, blood and blood products, and small intestines excluding distal ileum. These impacts include the potential for establishment of BSE in the United States and the projected consequences of any additional cases that might occur even without establishment. Therefore, the risk we evaluate includes both the likelihood of BSE establishment, and the impacts of cases that might occur even without establishment. The risk was evaluated qualitatively for all commodities and also quantitatively for additional live animal import scenarios. For the latter, the likelihood of establishment is measured by the disease reproductive rate (R_0). We also simulated the total number of animals in the United States that might become infected with BSE as a result of the importation of live bovines from Canada over the 20 years. Of the infected animals, those that we assumed that might have economic impacts were only the animals expected to live long enough to display clinical signs, as these are the most likely to be detectable with current testing methods. We have added this clarification to the Introduction of the revised risk assessment.

Hazard Identification

Issue: In response to Charge 2.a ("Does the analysis consider the relevant peer-reviewed studies, including both those that support the risk estimation's conclusions, and those that do not? If not, please indicate significant references that should be included."), one reviewer stated that

> "...essentially all of the information and assumptions regarding transmission, tissue distribution, presence or absence in blood or other organs etc. pertains to 'classical BSE.' Little is known about these parameters for 'atypical BSE cases' (see, for example, Beringue et al., 2006; Casalone et al., 2004; De Bosschere et al., 2004; Buschmann et al., 2006a; Buschmann et al., 2006b; Lloyd et al., 2004; Yamakawa et al., 2003)" (RTI 2007, p. 6-10).

Response: We agree that little is known about the specific parameters of the so-called "atypical BSE cases." In addition, we note the differences among the literature descriptions of these unusual BSE cases, thus leading to confusion over what is meant by the term "atypical BSE" (Beringue, et al. 2006; Casalone, et al. 2004; De Bosschere, et al. 2004; Buschmann, et al. 2006; Buschmann, et al. 2006a; Lloyd, et al. 2004; Yamakawa, et al. 2003). However, based on current research and the studies referenced by the reviewers, the understanding of the risk of transmission (and the definition of specified risk material (SRM)) has not changed, even when incorporating these recently identified unusual or so-called "atypical" BSE cases (OIE 2003).

In addition, the reviewer stated that "Arnold and Wilesmith (2004) support the assumption that most BSE infections occur in the first year of life" (RTI 2007, p. 6-10).

Response: We appreciate the reviewer's suggestion to include this relevant reference. We have added Arnold and Wilesmith (2004) to the list of references that provide evidence that infection most likely occurs in younger animals. We have also included a description of the study, which demonstrated that dairy cattle were most at risk of infection in the first six months of life.

Issue: In response to Charge 2.b ("Does the analysis accurately characterize the cited literature?"), a reviewer questioned our interpretations of two studies cited in the discussion of the ages of peak BSE susceptibility. Whereas we had included the study of Ferguson, et al. (1997) among sources that provided evidence that most cattle are exposed in the first year of life, the reviewer noted that the authors wrote that "the peak (of infection) occurs at one year of age, not at birth" (RTI 2007, p. 6-10). The reviewer also questioned our use of the verb "estimates" with regard to our characterization of the study by de Koeijer, et al. (2004).

Response: We listed the first study, by Ferguson, et al. (1997), among those that provided evidence that cattle had "… most chances of becoming infected during the first year of life." In this study, the authors applied curve-fitting models to epidemiological data to determine the most likely distribution of age-dependent susceptibility. We have clarified the risk assessment language to reflect that the listed references support the conclusion that calves had the most chance of exposure at or around the first year of life. However, given the weight of evidence from the other sources (e.g., Wilesmith, et al. 1988, Arnold and Wilesmith 2004), we do not change our conclusion that cattle are most susceptible when young, particularly during their first year. These studies also use mathematical modeling techniques, but conclude that peak susceptibility likely occurs during the first year of life.

With respect to the second study (de Koiejer, et al. 2004) noted by the reviewer, the study authors assumed, rather than suggested or estimated (as we stated), that "[s]usceptibility declines exponentially after the age of 4 months leveling off at 10% of the peak value." The reviewer also points out that "this is not a simulation model." By stating that the authors "suggested" or "estimated" the distribution of age-dependent susceptibility, we did not intend to imply that they were in fact demonstrating it. Rather, we were intending to point to their explicit assumption of such a distribution as an indication that in the absence of direct epidemiological or experimental data, the scientific community has accepted that this type of age-dependent distribution is likely. We have clarified the language of the risk assessment to better characterize and articulate the purpose of the citation.

Issue: Another reviewer stated that the models did not cover the issue of the potential risk of infectivity from animals that were disposed of on-farm. He noted that "some of the commonly-used disposal methods (burning/incineration, burial) are known to be ineffective in completely neutralizing BSE prions, and there may be possible environmental contamination and subsequent risk to cattle or other ruminants. Given the controversial hypothesis regarding scrapie in sheep and the onset of chronic wasting disease (CWD) in deer in Colorado (the connection between the first deer identified with CWD being those that were housed in a pen that held scrapie sheep several years earlier), this might be an area to consider in future risk assessments" (RTI 2007, p.6-18). Although this comment was made in the context of the models used in the assessment (Charge 4), we are addressing it in the Hazard Identification section, in that it relates to the larger biological context in which the models were developed and applied.

Response: Although the potential link described by the reviewer between scrapie in sheep and CWD in deer is of interest from the broader perspective of transmissible spongiform encephalopathies (TSEs), we did not account for this hypothetical exposure pathway in the risk assessment because the evidence to date strongly indicates that BSE is a food/feed-born disease, with no evidence of environmental transmission (Prince, et al. 2003; Wilesmith, et al. 1988; 1991; 1992). There are distinct differences among the animal TSEs. BSE in cattle (and overall) is very different from both scrapie in sheep and CWD in deer and elk. Despite strong evidence of environmental transmission of CWD, no such pathway has ever been identified for BSE.

Release Assessment

In this section we address the issues raised by the reviewers regarding evidence, assumptions, or methodologies presented in the Release section of the risk assessment. We first address

those comments that most directly apply to the estimation of prevalence in Canada, then to the determination of the date of effective enforcement of their feed ban (the primary mitigation on live animal imports imposed in the current rule), and the live animal import projections. Because of regions of overlap with the Exposure Assessment, some issues are addressed in that section. Also, the reviewers made minor suggestions regarding our use of various statistical terms (e.g., confidence interval). Where appropriate, we have made corresponding clarifications to the risk assessment.

Prevalence:

Issue: A reviewer suggested that the analysis needs to acknowledge the exogenous sources of BSE into Canada. As phrased by the reviewer (RTI 2007, p. 6-17):

> "For the assumption that BSE prevalence in Canada would decrease over the next 20 years until the disease is eradicated, the authors relied on compelling evidence from the U.K. experience with the ruminant feed ban and the resulting dramatic decrease in BSE prevalence in cattle. However, this did not address any issues associated with exogenous sources of BSE into Canada (imports from other BSE-affected countries). The Canadian prevalence model used for this analysis appears to assume no new exogenous sources of BSE. The dilution of risk due to current practices that reduce the likelihood of spread of prions through the Canadian cattle herd make this risk minimal at best, but it should be addressed for the sake of completeness."

Response: The prevalence estimation models use BSE surveillance data (test results from dead or slaughtered cattle) as inputs and therefore cannot differentiate whether the source of infectivity is endogenous (recycled) or exogenous (introduced). Also, because they are based on actual surveillance data, they cannot attempt to predict any changes in Canadian BSE prevalence over the next 20 years. The qualitative prediction of a drop in prevalence is based on the experience in the United Kingdom (UK) and does not assume that no additional infectivity can be introduced. In addition, the results of the U.S. Harvard model presented in our risk assessment illustrate that despite the recurrent release of "exogenous infectivity" (in this case, from Canada), the reproductive constant, R_0, remains well below one, indicating that the mitigations in place (particularly the ruminant feed ban) are effective in driving disease prevalence downward. Since the feed ban in Canada is very similar to that in the United States, we expect that any additional infectivity that may potentially enter Canada would fail to alter our predictions of a decrease in prevalence over time. For these reasons, we do not explicitly address the source of BSE infectivity in Canada as either endogenous or exogenous.

Issue: In response to Charge 1.b. ("Does the analysis adequately incorporate uncertainty and variability"), a reviewer remarked, "I am not in complete agreement with the statement '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.' This may well be true. However, there is a considerable amount of uncertainty associated with that conclusion" (RTI 2007, p. 6-8). Another reviewer made a similar comment, "[p]age 22 – not sure that the BBC method provides a more precise estimate, probably just more realistic" (RTI 2007, p. 6-26).

Response: In statistical terms, the BBC estimate is more precise than the BSurvE estimate in that the former has a smaller estimated confidence interval. Precision is distinct from accuracy. Different modeling assumptions would result in different prevalence estimates which may be more or less accurate predictors of future prevalence. We have inserted this clarification as a footnote in the risk assessment.

Prevalence attachment (Attachment 1):

Issue: On p. 6-28, a reviewer stated that "a minor point but the statement 'converging to local rather than global maxima' [on p. 14 of the prevalence attachment] is not really correct. This implies convergence to a number – the convergence is to a distribution."

Response: The reviewer's point is taken; however, no change to the risk assessment is required in response to the comment. The local rather than global maxima refer to the numerical value of the likelihood function (corresponding to the distribution) that the Monte Carlo Gibbs procedure is attempting to maximize by iteratively searching through the input parameter space. If all goes well, the search stops when the value of the likelihood function reaches a global peak. However, the search may stop at a false summit if a local plateau is sufficiently broad. For this reason, the non-iterative Sampling Importance Resampling (SIR) method was used to check the BBC model results obtained using the Gibbs sampling procedure performed by WinBUGS.

Issue: A reviewer commented that on "[p]ages 20 and 21 – the WinBUGS code could be better documented – where do the numbers 1,194,932 and 5,979,757 come from? What about the proportions standing? Ideally, the code should be able to stand alone without the document and be utilized by another researcher/government official" (RTI 2007, p. 6-28).

Response: We provided the appendix to the Prevalence attachment to illustrate the methodology used. Although the values used in the code can be found elsewhere in the attachment (e.g., APHIS 2006a, pp. 2-3 and Table 1, shows that 1,194,932 represents the number of female cattle under one year of age, and 5,979,757 represents the number of cows two or more years of age), the appendix on it own was not intended to serve as a stand-alone guide to rerunning the model. Although recreating the analysis would necessarily require considerable time and effort (including an investment in becoming proficient with the publicly accessible BSurvE model), the results are reproducible based on the documentation presented in Attachment 1 and its appendix.

Issue: In reference to statements made in the prevalence attachment regarding lack of independence across birth cohorts, a reviewer stated, “The biological reasons for a single prevalence value need to be explored further” (RTI 2007, p. 6-18).

Response: First, it should be noted that the BBC prevalence estimate incorporates a decline in birth year cohort prevalence for the first five years after the Canadian feed ban was introduced. After five years, prevalence is assumed to remain constant across birth year cohorts under both the BBC and BSurvE models used in the analysis. Regardless of which prevalence estimate (BBC or BSurvE Prevalence B) is used as a model input, the exposure assessment then treats the probability of infection as constant over the next 20 years. If the probability of infection were to remain constant, BSE prevalence would vary randomly but exhibit no trend over time. For exposure to remain constant over time, infectivity losses due to inactivation, sequestration (e.g., burial), and exports would have to equal infectivity gains due to amplification, mobilization (the release of sequestered material, making it available for uptake), and imports. APHIS does not posit a biological or any other rationale for how the probability of infection would remain constant over the next 20 years in light of the results of feed bans. Instead, like Reviewer A, APHIS judged that "[i]t was prudent not to attempt to predict the future decline in the Canadian BSE prevalence" (RTI 2007, p. 6-6). As Reviewer B notes, in light of the results of feed bans, "using a single prevalence estimate resulted in a conservative approach to the final risk assessment, and they [APHIS] interpreted their results with this in mind" (RTI 2007, p. 6-18).

Assumptions used in the prevalence estimates:

Issue: A reviewer commented on the “[g]eographic clustering of cases in Canada. I assume that zoning is not a realistic mitigation to consider, even though the epidemiologic data (page 12) are highly suggestive of clustering of cases in Alberta province” (RTI 2007, p. 6-23).

Response: As the reviewer noted elsewhere (RTI 2007, pp. 6-26 and 6-27), with so few total cases, determining statistically significant differences in prevalence among cohorts is not possible. (Alternatively, the differences would have to be quite large to provide a reasonable likelihood of detection.)

Through May 2007, reported BSE cases have originated in three western provinces: Alberta (8 cases), British Columbia (2 cases), and Manitoba (1 case). No cases have been reported through May 2007 in the eastern provinces. Intuition might suggest that the BSE prevalence is higher in Alberta. However, Alberta contains approximately 40 percent of the Canadian cattle herd. Other factors being equal, BSE is more likely to be detected in regions with large cattle populations.

Apart from the detected cases, geographically disaggregated data on BSE surveillance and Canadian cattle population demographics are not available. However, assuming that the total BSurvE points accumulated through August 15, 2006 (APHIS 2006a, Table 4) were collected proportionally to the cattle population size in each province results in the allocation of the random sample size equivalents (BSurvE points) presented in Table 1.

Table 1. Allocation of BSurvE Points among Provinces Proportional to Herd Size

Province	Cattle (000)*	Percent	BSurvE Points	BSE Cases**
Alberta	6,300.0	38.8%	594,858.4	7
Manitoba	1,720.0	10.6%	162,405.8	1
British Columbia	830.0	5.1%	78,370.2	1
Saskatchewan	3,450.0	21.2%	325,755.8	0[+]
Ontario	2,203.9	13.6%	208,096.6	0
Quebec	1,455.0	9.0%	137,384.0	0
Nova Scotia	107.0	0.7%	10,103.2	0
New Brunswick	90.5	0.6%	8,545.2	0
Prince Edward Island	84.5	0.5%	7,978.7	0
Newfoundland and Labrador	9.1	0.1%	859.2	0
Total	16,250.0		1,534,357	9

*Source: Statistics Canada (2007)

**BSE cases reported through August 2006 were included in APHIS (2006a)

[+]The BSE case confirmed in May 2003 was born in Saskatchewan but reported in Alberta.

Based on this allocation of evidence, a binomial likelihood ratio test (Fleiss, et al. 2003) fails to reject the hypothesis that the provinces have the same BSE prevalence. (That is, the result provides no basis for concluding that BSE prevalence varies among provinces.) Furthermore, depending on the method used to estimate provincial BSE prevalence, the test indicates that 11-20 BSE cases would have to have been observed in Alberta (or 4-7 cases in British Columbia) before rejection of the hypothesis that the provinces all have the same BSE prevalence. Furthermore, adding the Alberta and British Columbia BSE cases confirmed in February and May 2007, respectively, does not alter the conclusion that there is no statistical basis for concluding that BSE prevalence varies among provinces. If geographic heterogeneity in Canadian BSE prevalence does exist, the differences across regions are so small that they would be undetectable based on available evidence.

Issue: A reviewer noted that "[a]ge specific mortality and slaughter rates are unavailable for the Canadian cattle population, so cattle population demographics for the US were applied to the Canadian cattle population. If the estimated US cattle population demographics are reasonable then their use for the Canadian population is acceptable. It appear[s] that this is the best information available. This, however, is a source of uncertainty" (RTI 2007, p. 6-12).

Response: We agree that this assumption represents a source of uncertainty; however, as the reviewer indicates, the assumption was based on the best information available. As noted on page 2 of Attachment 1 (APHIS 2006a), "[i]t is reasonable to assume that the same rates would be applicable to Canada as the cattle industries in both countries are virtually identical. For example, the relative proportion of beef and dairy cattle (80 percent and 20 percent, respectively), management practices (such as breeding, feeding and rearing), and slaughtering practices are essentially the same in both countries." Because age-specific mortality and slaughter rates data are unavailable for the Canadian cattle population, we have no empirical basis for making an alternative assumption. Another reviewer commented that "using U.S. estimates for the age structure and stratification of Canadian cattle was valid" (RTI 2007, p. 6-17).

Issue: A reviewer stated that [o]ne source of variability would be clustering of cases at the herd level, or geographic variability. Perhaps, explicitly listing potential sources of variability that were considered and justification for not including other sources of variability would be helpful" (RTI 2007, p. 6-28).

Response: A cohort of animals may be defined by any number of common characteristics, such as birth year, geographic region, market class, or otherwise. There is no definitive answer to how narrowly or broadly a cohort should be defined, and there is no limit to the sources of variability

that could be hypothesized (e.g., birth cohorts within a herd, calves borne by a cow, etc.). For a given level of surveillance, stratification of the population (as discussed in response to an earlier comment on potential geographic heterogeneity) will lead to a loss of power due to smaller effective sample sizes (Bohning and Greiner 2006). Consequently, as cohorts are more narrowly defined, it becomes more unlikely that heterogeneity (if it exists) will be detected given the available surveillance data. Furthermore, hypotheses pursued in the epidemiologic investigation of BSE cases to identify the likely source of exposure are not necessarily relevant to the risk assessment of imports. For example, because animals are often moved over time, calves from a suspected cluster of infections may be geographically dispersed prior to slaughter, the onset of clinical symptoms or export. Therefore, for the purposes of this import risk assessment, the birth site is not necessarily informative. Given the long list of potential variables that have not been incorporated for the reasons provided, we see no reason to explicitly list them.

Issue: A reviewer commented that "[t]he BBC model assumes that the rate in the decline in the incidence of BSE following the [meat and bone meal] MBM ban in Canada is the same as that seen in the UK following its first feed ban. I think it is correct to assume the Canadian feed ban will eventually have some effect in reducing if not eliminating new cases but the rate at which that happens cannot be precisely estimated. The rate in decline may or may not be the same as that seen in the UK" (RTI 2007, p. 6-9).

Response: We agree with the reviewer that there is uncertainty regarding the applicability of the rate of decline in BSE prevalence in the UK to Canada. For that reason, we have formally addressed this uncertainty by considering the result of the BSurvE Prevalence B model (Wilesmith, et al. 2004), which makes no assumptions about the applicability of the rate of the effect of the feed ban in the UK to estimate of Canada's BSE prevalence.

BSE prevalence and live animal release conclusions:

Issue: In response to Charge 1.a. ("Does the analysis clearly convey the expected risk of establishment of BSE in the United States…"), a reviewer suggested that we address the amount of uncertainty that is associated with the conclusion that the likelihood of releasing BSE into the United States from Canada via importation of live bovines is extremely low. He suggested that we report and use the 95th confidence levels throughout the assessment. In the context of our consideration of uncertainty, he also specifically questioned "if the likelihood of importation of ca. 9 BSE infected cattle (1.31 million cattle imports* 6.8*10^-06, the upper 95% confidence limit of the BSurvE prevalence estimate), a plausible scenario, represents an extremely low likelihood of release" (RTI 2007, p. 6-5).

Response: As indicated in Table 2 below (identical to Table 3 from the risk assessment (APHIS 2006) and Table 5 from Prevalence Attachment 1 (APHIS 2006a)), uncertainty between prevalence estimation models (BBC or BSurvE) is greater than the statistical uncertainty within prevalence estimation models (represented by confidence levels for a given model). Therefore, uncertainty about prevalence is addressed by considering the two expected (average) prevalence estimates obtained with different models. This reviewer also comments that the expectation that prevalence remains stable at the lower level estimated by the BBC model over the next 20 years is "a very pessimistic assumption" (RTI 2007, p. 6-5). Similarly, another reviewer states that it is "very reasonable" to assume that BSE prevalence in Canada will decrease over the next 20 years until the disease is eradicated (RTI 2007, p. 6-25). If these assertions are correct, then assuming that prevalence remains stable at the 95 percent (or 99 percent) confidence level estimated by the BSurvE model over the next 20 years would simply result in a more extremely pessimistic assumption. A reviewer comments, "[i]t should, however, be pointed out that the other pessimistic assumptions in the Exposure Assessment model (for example no decrease in BSE prevalence over the next 20 years) would likely override any underestimate of the present BSE prevalence due to using the mean BBC prevalence estimate" (RTI 2007, p. 6-9). Therefore, we have elected not to rerun the exposure model using the 95 (or 99) percent confidence level estimated by the BSurvE model.

Table 2. Results of prevalence calculation (2006)

Prevalence in adult cattle population	**Bayesian birth cohort method (BBC) with UK feed ban data**	**BSurvE Prevalence B estimate without including feed ban data**
Expected value (mean)	$6.8*10^{-7}$	$3.9*10^{-6}$
95th percent confidence level	$1.1*10^{-6}$	$6.8*10^{-6}$

The reviewer's related comment on the accuracy of our conclusions regarding the likelihood of release in the face of such highly pessimistic scenarios indicates the need to be more transparent and to clarify our characterization of "release" in general. This term was not clearly defined in the assessment and could be considered, as he appears to suggest, as the probability of introducing any BSE infectivity by importing one or more infected cattle over time. This interpretation, however, is not a particularly useful way to consider the overall likelihood of release. A more meaningful approach for our purposes, and one that is used within the risk assessment, is to consider the probability of introducing any BSE infectivity (e.g., by importing one or more infected cattle over time), frequency (e.g., the number of imported infected animals per year), and magnitude (e.g., both the number of infected animals over the period of analysis and the amount

of infectivity these animals are likely to carry). For purposes of this analysis, we incorporate all of these points in the consideration of the likelihood of release. We have made changes to the risk assessment to reflect this meaning.

Issue: In response to Charge 1.b. ("Does the analysis adequately incorporate uncertainty and variability…"), a reviewer suggested considering another scenario to incorporate a 20 percent drop in Canadian BSE prevalence within the next five years (RTI 2007, p. 6-21).

Response: The modeled quantitative scenarios, in which we assumed that Canadian BSE prevalence remains constant at the current level for the next 20 years, demonstrated that the estimated reproductive rate (R_0) remains below 1.0. Consequently, considering the reviewer's proposed scenario in which Canadian BSE prevalence declines by 20 percent within the next five years would result in a lower than previously estimated risk of BSE establishment in the United States as a result of Canadian imports. This scenario is consistent with the most likely, qualitative scenario in which Canadian BSE prevalence is expected to decrease through time.

Issue: A reviewer stated that the BSE risk estimates should be updated to include the Canadian case detected in February 2007 (RTI 2007, p. 6-23).

Response: Updating the risk estimates to account for recent BSE cases in Canada would require revising the prevalence estimates in light of these cases and then running the exposure model using the revised estimates. To determine the necessity for rerunning the exposure model, we first determined if the prevalence estimates themselves have changed in the face of the more recent cases.

The prevalence attachment to the risk assessment (APHIS 2006a) estimated Canadian BSE prevalence based on a 7-year surveillance period through August 15, 2006. This surveillance period included the detection of nine BSE cases of Canadian origin reported through August 2006. Based on surveillance conducted from August 16, 2006, through April 2007, Canada detected one BSE case born in 2000 and another born in 2001 (CFIA 2007). The BSE prevalence estimation methods used by APHIS (2006a) require detailed data to stratify tested cattle by age and cause of death (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect) that are unavailable for the more recent surveillance period. However, we can assess the previous Canadian BSE prevalence estimates by adding the two additional cases without changing the BSE surveillance points accumulated by Canada during the 7-year surveillance period through August 15, 2006 (APHIS 2006a, Table 4). This approach results in a revised table

of BSurvE points and BSE cases by birth year cohort that reflects a total of 11 BSE cases of Canadian origin reported through April 2007 (Table 3).

Table 3. BSurvE points and BSE cases by birth year cohort

Birth year	BSurvE Points	BSE Cases
1991	24,737	1
1992	35,814	0
1993	61,914	0
1994	115,950	0
1995	183,528	0
1996	225,473	2
1997	217,155	2
1998	173,111	1
1999	142,290	0
2000	150,111	3
2001	128,565	1
2002	59,090	1
2003	13,894	0
2004	558	0
2005	2,170	0

Using the same methods described in APHIS (2006a), we obtain updated Canadian BSE prevalence estimates:

Bayesian Birth Cohort (BBC, WinBUGS): 90 percent confidence interval = 0.47-1.2 per million
BSurvE Prevalence B: 90 percent confidence interval = 3.0-8.0 per million

Because the updated confidence intervals contain the previous expected value estimates of 0.68 per million (BBC) and 3.9 per million (BSurvE Prevalence B) (APHIS 2006a), we conclude that the prevalence estimates used in the October 2006 risk assessment are not sensitive to the detection of these additional cases (APHIS 2006). Moreover, the likelihood of release of infected animals is also dependent on the number and, qualitatively, on the age of the animals imported. Given that the updated projection estimates prepared by USDA's Economic Research Service (ERS) reflect only a small increase in numbers of animals (125,000 over the 20 years of the analysis), the quantitative risk estimation would not differ significantly from that already estimated. Also, because the updated projections show a proportional and absolute drop (relative to the projections published in the original risk assessment) in the number of older cull cattle in the first

few years of the 20-year period of analysis, we qualitatively anticipate that even fewer infected animals will be imported. We do not expect a greater likelihood of release than initially concluded. Therefore, we see no need to rerun the exposure model to update the risk estimates.

Issue: Also in response to Charge 1.b., a reviewer stated, "[t]he assumption of decreasing prevalence over time using the qualitative model is appropriate and the authors are accurate in their statement that this decrease in the prevalence can not be quantified. However it was not clear from the presentation that the final outcome using the quantitative model did not use this assumption" (RTI 2007, pp. 6-20 to 6-21).

Response: The quantitative analysis assumes no change in Canadian BSE prevalence over 20 years (see Executive Summary of the APHIS risk assessment (APHIS 2006, p. 8) and Section III.D.1.).

Issue: A reviewer noted that "[t]he use of identical methodologies in the current risk assessment and the peer reviewed BSE prevalence document for the U.S. theoretically allows indirect comparisons between BSE prevalence in the two countries" (RTI 2007, p. 6-23).

Response: This comment is correct. The use of identical methodologies permits comparisons between BSE prevalence in Canada and the United States. However, such a comparison does not provide additional information for the purpose of evaluating the likelihood of establishing BSE associated with imported bovines and bovine products from Canada.

Date of Effective Enforcement of the Feed Ban:

In this section, we address comments that the reviewers made regarding the determination of the date of effective enforcement of Canada's feed ban. We note that some comments overlap with other sections, such as BSE prevalence in Canada.

Issue: A commenter noted that "…unlike the situation when the US estimate was done there is evidence that the Canadian feed ban was not fully effective when the estimate was done (CFIA, 2006)" (RTI 2007, p. 6-4).

Response: We do not equate a fully effective feed ban with the absence of any additional cases. Effective enforcement of a feed ban does not prevent all instances that may contravene that feed ban, either accidentally or intentionally, just as isolated transgressions of U.S. laws do not necessarily constitute ineffective enforcement of those laws. As we discussed in our risk

assessment, detection of BSE in an animal born after the date a 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 fact, most other countries that have experienced cases of BSE, have reported similar cases. Nevertheless, despite such occurrences, a feed ban will be effective in decreasing the transmission of disease (Heim and Kihm 2003).

Import projections:

Issue: In response to Charge 3.b. ("Examine the assumptions regarding the import projections for live bovines from Canada"), a reviewer suggested "that a clearer statement should be made about how these projections were made e.g. combination of statistical (time series analysis?) and expert opinion (based on similar historic events?)" (RTI 2007, p. 6-25).

Response: The projected imports by age and use class were prepared for APHIS by USDA ERS. These values are based on USDA Baseline projections, with specific factors considered based on the regulatory changes proposed. Additional details are provided in Appendix 1 of the Regulatory Impact Analysis and Final Regulatory Flexibility Analysis and are summarized in the revised risk assessment.

Issue: In response to Charge 3, a reviewer stated that "more discussion/evidence is needed to support the assumption of declines in imports of live bovines from Canada. For example, increases in imports of live bovines could affect the risk estimates which could be discussed in the report" (RTI 2007, p. 6-17).

Response: We assume that the reviewer is referring to the initial drop in imports projected from 2007 to 2009. This drop actually reflected the depletion of an inventory "bubble," particularly among cull cattle that have been prohibited entry under current regulations (APHIS 2006). Based on market forces, starting in 2010 the projected imports were expected to increase, followed by some dips due to cattle cycling. However, in the revision of the projections prepared by ERS (see Appendix 1 of the Regulatory Impact Analysis), updated projections that incorporate more recent trade data and projections (particularly the impact of the age verification requirement on the number of imported cull animals), indicate that no such initial bubble is anticipated. In fact, the projected number of imported animals increases virtually continuously over the next 20 years. Since the initial drop to which the reviewer was apparently referring in his comment is no longer present in the updated projections, we will not change the risk assessment to explain the original drop from 2007-2009. However, we have explained the updated projections in the Updates section of the revised version.

Issue: In response to Charge 3.b, a reviewer commented that "[i]n the projections, there is no reference to cost so I assume that an inherent assumption is that there is no substantial price difference between the U.S. and Canadian cattle markets after allowing for transportation and handling costs" (RTI 2007, p. 6-25).

Response: Because this subject is outside the scope of the risk assessment, we have not modified the risk assessment in response to the comment. We note here, however, that the reviewer's interpretation that no price difference exists is incorrect. For example, currently the cost of cull cattle from Canada is lower (even with transport costs) than cull cattle from the United States. This point is addressed in the Regulatory Impact Analysis and Final Regulatory Flexibility Analysis (APHIS 2007).

Issue: The same reviewer noted that he "found an FAO analysis from December 2006 (FAO, 2006) that refers to BSE impacts on animal markets. In the FAO document, there does not seem to be anything that is inconsistent with the ERS economic analysis but perhaps some of the issues raised could be included and the document referenced" (RTI 2007, p. 6-25).

Response: As expected, the removal of trade restrictions by Japan and other countries is predicted by the study to which the reviewer refers (FAO 2006) to accelerate the increase of North American beef output. Because of fairly modest increases in production, coupled with a rise in exports, the FAO model predicts a five to 10 percent increase in domestic beef prices through 2015. Although this finding is reasonable, it has little bearing on the evaluation of the incremental consequences of additional BSE cases. Accordingly, we have not included it in the revised risk assessment. Regarding the reviewer's reference to the "ERS economic analysis" (by which we assume he means the import projections), although the ERS staff members that prepared the import projections were familiar with the FAO study, among others, because of underlying assumptions which were inconsistent with the U.S. baseline model, they elected not to incorporate it into their analysis.

Exposure Assessment

Exposure model:

Issue: A reviewer stated that "[i]t would be informative if R_0 would remain below 1 if the simulation were done using the 95 CL for the BSE prevalence obtained with the BSurvE model" (RTI 2007, p. 6-6). This suggestion is nearly identical to one by another reviewer who suggested that we use the 99th percentile for the same purpose. He remarked that "[b]ecause prevalence is the main factor influencing the estimated number of introduced BSE infected animals, it would be

appropriate to consider using the 99% limits for prevalence in the model. I think that the 99th percentile values for the 2 prevalence estimates should be run in both the BSurvE and BBC models just to reaffirm that R_0 is still less than 1, even in this extreme case" (RTI 2007, p. 6-23). In a similar comment, the same reviewer stated that "[t]he analysis indicates that R_0 is consistently low but it might be helpful to explicitly determine how many BSE infected animals would need to be introduced into the U.S. for R_0 to approach 1, i.e., for BSE to cycle given the mitigations in place" (RTI 2007, p. 6-23).

Response: The exposure model's sensitivity analysis scenario for the prevalence estimate demonstrated that a greater than five-fold increase in release resulted in less than a doubling of R_0 to a mean value of 0.075.[1] Given that this over-estimate remains significantly less than 1, we conclude that rerunning the model to demonstrate that R_0 remains less than 1 at the 95 or 99 percent confidence level of the BSurvE prevalence calculation is unnecessary.

In addition, the reviewers have indicated that assuming constant prevalence (at either of the considered levels) over 20 years is in itself a very pessimistic assumption. We see no need to test even more extreme assumptions. Similarly, since determining the number of imported infected animals that may be necessary for R_0 to approach 1.0, as a reviewer suggested, does not realistically inform the decision at hand, we are not adding those scenarios, either.

Issue: In response to Charge 4.b.ii.b ("Review updated parameter estimates"), a reviewer stated that our assumptions regarding the disposition of MBM are not fully justifiable and that we may want to consider further evidence for these assumptions. In particular, the reviewer states that he does not believe that all SRMs are removed (RTI 2007, p. 6-22).

Response: We think that the reviewer's concern regarding the disposition of MBM may be based on a misunderstanding of the underlying assumptions. We do not assume that all SRMs are removed from MBM. In fact, we assume that infectivity from undetected cases is most likely to exit the system via rendered SRMs in prohibited MBM. To the extent that some of this material may cycle back to cattle (such as via misfeeding) new animals may potentially be exposed. In fact, the base case of the exposure model demonstrates that over the 20 years of the analysis, roughly two more animals may be exposed due to such recycling.

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[1] The base case scenario included a prevalence of $0.68*10^{-6}$ and resulted in a mean R_0 value of 0.044. The sensitivity analysis incorporating the BBC estimate of $3.9*10^{-6}$ resulted in a mean R_0 value of 0.075.

Issue: Two reviewers suggested including a pathways diagram to represent the exposure model (RTI 2007, pp. 6-22 and 6-24).

Response: We appreciate the suggestion for inclusion of a pathways diagram and agree that a visual representation can often improve clarity. However, in this instance, a diagram that appropriately represents the model would become very complex. We do not believe it would add to the clarity of the document, and in fact could be distracting. The audience for this document is very wide-ranging, including the general public, and we therefore elected not to include an overly complex figure that could distract from the understanding of the assessment.

Blood and blood products:

Issue: A reviewer suggested that we acknowledge the uncertainty in our conclusions about exposure to BSE via imported blood and blood products (RTI 2007, p. 6-7).

Response: We have modified the conclusions for the blood and blood products section of the exposure assessment to indicate that they are drawn in the face of a certain amount of uncertainty. Specifically, the concluding sentence of Section IV.B. is now:

> Therefore, despite the uncertainties of applying data collected on other TSEs and host species, the strength of the evidence that we have collected allows us to conclude with adequate certainty 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.

Intestines:

Issue: The reviewer suggested that we include a similar statement to acknowledge our uncertainty regarding exposure that might result due to imports of small intestines (RTI 2007, p. 6-7).

Response: As in response to the preceding suggestion, we have modified the conclusions for the intestines section of the exposure assessment to indicate that they are drawn in the face of a certain amount of uncertainty. Specifically, the concluding paragraph of section IV.C. is now:

> Despite the uncertainties associated with the precise likelihood of cattle consuming imported bovine small intestines from Canada, given the available ~~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.

Consequence Assessment

Issue: A reviewer commented that "[o]ne argument that might be made is that introduction will not lead to an establishment of a cycle of infection but may extend the temporal occurrence of the number of cases of BSE in the U.S. Are there any adverse economic effect[s] associated with this outcome? One possibility is that testing levels might need to be maintained for a longer time than if there were no more introduced and detected BSE cases. Market access and prices for beef and beef products might also be adversely affected" (RTI 2007, p. 6-23).

Response: The APHIS risk assessment did not consider endogenous levels of BSE in the U.S. cattle herd; however, continuous exogenous inputs of BSE infectivity from Canada (as is assumed in the less likely quantitative scenarios of the risk assessment) or any other source would extend the time to eradication of the disease in the United States. Although the incremental duration of the extended time to eradication is unknown, we expect that it would have little or no practical effect on the potential economic impacts of BSE in the United States. We note that the exposure model, which incorporates several risk-inflating assumptions, estimates that over the 20 years of the analysis there will be less than one clinical case of BSE in the United States as a result of the cattle imported from Canada. Given that the United States has already detected three BSE cases (two in native cattle), we do not expect any incremental impact (from a lengthened period of testing or from additional market impacts) of this very small number of potential additional cases. This point is described in detail in the consequence section of the risk assessment.

Issue: A reviewer states that the "consequence assessment, while likely correct, is somewhat superficial given the gravity of BSE. The consequences of importing … BSE infected cattle or cattle products would be very different depending on which segment of the cattle industry or population was affected" (RTI 2007, p. 6-7).

Response: We acknowledge that the impacts on industry may be very different depending on which segment of the cattle industry or population is affected; however, USDA-ERS studies (Mathews, et al. 2006; Kuchler and Tegene 2006) indicate that consumer demand for beef in the United States remains strong despite cases identified to date. Moreover, as we explained in the Consequence section of the risk assessment, we do not expect additional trade or regulatory impacts in the event of the detection of additional BSE cases in the United States. As a

consequence, we expect a negligible incremental impact overall and on the various segments of the cattle industry in the unlikely event that any additional BSE cases would result from the importation of cattle and their products from Canada. We have strengthened our initial discussion of the absence of expected effects on consumer preference by including descriptions of the sources cited above. Otherwise, we are not making changes to the risk assessment in response to this comment.

General Issues

Issue: One reviewer requested greater attention to uncertainty throughout the document. Some of his concerns were addressed under discussions of issues regarding specific sections of the document (i.e., exposure via blood or intestines). Here we address the more general comments, such as "uncertainty is consistently underplayed if not ignored" and "it would perhaps be useful to actually list the sources of uncertainty in each of the sections" (RTI 2007, p. 6-9). Another reviewer suggested that we list all the model inputs considered to be variable (RTI 2007, p. 6-24).

Response: We disagree with the reviewers. Though not always addressed as distinct lists, uncertainty and variability are incorporated throughout the risk assessment. The models used in the risk assessment are complex with a large number of inputs, which, like for most models, may be somewhat uncertain and/or variable. However, preparing a comprehensive list of uncertain and/or variable risk assessment model inputs is not necessary. In our judgment, the inputs are better discussed in the context of how they are used in the model.

All of the BSE prevalence estimation model inputs represent best available estimates of either a variability distribution (e.g., BSE incubation period, cattle age structure) or a parameter value (e.g., number of adult animals in the herd, age of a BSE tested animal). Consequently, the calculated confidence intervals represent statistical uncertainty about current BSE prevalence related to random sampling error. The major source of uncertainty regarding BSE prevalence in the current standing cattle population was considered to be the effect of the Canadian feed ban. This uncertainty was addressed by considering two BSE prevalence estimation models: the BBC model, which incorporates an estimate of the effect of the feed ban based on the UK evidence, and the BSurvE Prevalence B model, which makes no assumptions about the effect of the feed ban. Variability also entered into the prevalence calculation in that the BBC prevalence model assumes that birth year cohort prevalence declined during the first five years after Canada introduced a feed ban in 1997. Thereafter, both the BBC and BSurvE models were used to obtain the expected proportion of BSE infected animals, which is assumed to remain constant over time in the quantitative risk analysis.

Another component of the release assessment, for which uncertainty has not been addressed, is the import projections. As described in detail in response to another peer review comment, these projections were prepared by USDA ERS and based on USDA baseline projections and a broad array of expert opinion. Because they are projections, they are uncertain. This uncertainty has been reduced somewhat by incorporating more recent data into the 2007 import projections, prepared for the final rule. Based on these updates, we expect lower numbers of older animals to be imported in the early years of the rule's implementation. The total imports over the entire 20 years of the analysis are only slightly (125,000 animals) higher than the original and so do not confer significant additional magnitude of release ($125{,}000*0.68*10^{-6}=0.085$ cases; $125{,}000*3.9*10^{-6}=0.49$ cases). Therefore, although the import projections are somewhat uncertain, reduction of this uncertainty has not significantly changed our release estimates or conclusions.

The projections used in the original analysis incorporated temporal variability across years due to the cattle cycle. The variability considered did not include possible but less likely extremes (shocks), such as a temporary spike in slaughter rates due to severe weather.

The parameters for the exposure model have been described in earlier documents (Cohen, et al. 2003). These documents explicitly examined the effects of uncertainty in key parameters in their respective sensitivity analyses. The version of the Harvard model performed for this rule included a sensitivity analysis to examine the uncertainty of several parameters – some of which were included in earlier models, and some of which were new parameters (e.g., the amount of chicken litter incorporated into ruminant feed and the Canadian BSE prevalence estimate). Of the uncertain parameters examined, Canadian BSE prevalence over the next 20 years was the most significant source of uncertainty for the model. This uncertainty contains two components: the estimate of prevalence in Canada's current standing cattle population, and how prevalence of BSE in Canada will change over time. This latter component was not treated quantitatively and its uncertainty was, therefore, not explicitly analyzed in the sensitivity analysis. Variability in this parameter was addressed, however. Assuming constant prevalence over the next 20 years, the simulated number of BSE infected cattle imported each year still varies because it is a combination of the predicted import volume (which varies as described above), and the sampling variation (using a Poisson distribution) about the expected prevalence value. This source of variation has already been described in the risk assessment.

In conclusion, rather than performing a comprehensive uncertainty analysis in which all model inputs are treated as statistical distributions, we identified and evaluated the potential

contributions to variability and uncertainty that we deemed most relevant to our analysis. Given that the uncertainty about the key inputs to the risk assessment models has been considered, we agree with the reviewers that further uncertainty analysis will not affect the conclusions of the risk assessment.

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