March 2007

Peer Review of the Assessment of BSE Risk Associated with the Importation of Certain Additional Commodities from BSE Minimal Risk Regions (Canada)

Final Report

Prepared for

U.S. Department of Agriculture
Animal and Plant Health Inspection Service
Riverdale, MD

Contracting Officer's Technical Representative

Chuanfa Guo
U.S. Department of Agriculture
Food Safety and Inspection Service
Washington, DC

Prepared by

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Research Triangle Park, NC 27709

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RTI International is a trade name of Research Triangle Institute.

Contents

Executive Summary

The Office and Management and Budget (OMB) requires a peer review for important scientific information to ensure the quality of scientific and technical research and guide improvements in the draft before federal agencies disseminate it (OMB, 2004). The Animal and Plant Health Inspection Service (APHIS) was interested in conducting a peer review of their risk assessment of BSE associated with the importation of certain additional commodities from BSE minimal risk regions (currently only Canada). APHIS requested RTI International's support in conducting a peer review conforming to OMB's guidelines (OMB, 2002, 2004) under RTI's task order contract with the Food Safety and Inspection Service (FSIS).

Specifically, APHIS requested a peer review to ensure that the proposed regulatory changes to further ease import restrictions on certain commodities from BSE minimal risk regions is based on a scientifically sound risk assessment. RTI identified four experts and conducted the peer review according to the statement of work. We present these four reviews in Section 6.

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 provided specific suggestions to make the risk assessment more scientifically accurate. They recognized that the results of such modifications will not change the overall conclusions of the analysis because several assumptions made in the analysis represent worst case scenarios. Across all aspects of the analysis, reviewers focused the most attention on estimating the prevalence of BSE in Canada. One reviewer suggested that the analysis needs to acknowledge the exogenous sources of introduction of BSE into Canada, another reviewer suggested using a higher value for prevalence, and a third suggested reporting and using 95th percent confidence levels for the prevalence estimates throughout the report to better qualify the uncertainty associated with the risk estimates.

Another set of comments focused on predicting future BSE prevalence in Canada and the effect of the feed ban on future prevalence. Overall, all reviewers agreed that the prevalence of BSE in Canada will likely decrease over time. They also agreed that the evidence from the United Kingdom (UK) and Europe that the feed ban is effective is reasonable to consider in the case of Canada. However, reviewers appreciated that APHIS assumed a worst case scenario in which BSE prevalence remains unchanged at the current level because it makes the results of the risk assessment more robust. Reviewers suggested alternative approaches to model reduced BSE prevalence in the future, but these suggestions are more in response to scientific interest than informing policy making regarding the risk of BSE from Canadian imports. One reviewer raised the possibility that newer BSE prevalence estimates may be needed if any new cases of BSE are detected in Canada in the future.

A final set of comments refers to recommended improvements in the analysis and presentation of the results in the report. Reviewers found the executive summary useful in interpreting the results and uncertainty in the results, as well as describing the overall approach (sometimes more useful than the main report itself). They provided various specific suggestions to improve the report further. For example, a couple of reviewers

suggested including a flow chart or a pathways diagram to represent the exposure model. Reviewers also suggested listing the inputs and specific risks systematically with a proper description of the variability and/or uncertainties associated with them. Reviewers desired more discussion of uncertainty in the main report while acknowledging a reasonably well-done job in the executive summary. A more systematic uncertainty analysis would be desirable from a theoretical perspective, but as a practical matter this analysis will not affect the conclusions that the risk of BSE introduction and establishment in the United States due to imports of certain commodities from Canada is negligible.

1 Background and Objective

RTI International coordinated the external peer review of the risk assessment for BSE introduction from importation of certain commodities from minimal BSE risk regions (or specifically, Canada) as requested by the U.S. Department of Agriculture's Food Safety and Inspection Service (USDA, FSIS) and the Animal and Plant Health Inspection Service (APHIS) under this task order. In this report, we present background information on the peer review, describe the review process, present the charge to the reviewers, introduce the reviewers, and include the four peer review reports.

APHIS has proposed amending the regulations to allow the importation of certain additional commodities from regions that present a minimal risk of introducing BSE into the United States – currently, only Canada. APHIS instituted import regulations related to BSE first in 1989 and subsequently revised these in response to additional knowledge about BSE. A final rule published in January 2005 established criteria to categorize BSE minimal risk regions, established conditions under which certain ruminants and ruminant products could be imported from minimal risk regions, and recognized Canada as a BSE minimal risk region.

Now, APHIS is proposing to further ease import restrictions on certain additional commodities from BSE minimal risk regions based on a risk assessment specific to the commodities in question. The risk assessment demonstrates that the proposed actions will continue to protect against the introduction and establishment of BSE in the United States. Therefore, this risk assessment is scientifically highly important and deserves an

external peer review as per Office and Management and Budget (OMB) (2004) guidelines.

The objective of the peer review is to determine whether the risk assessment is accurate, complete, and transparent; the application of external assessments or models is correct, the assumptions are justified; and international standards (e.g., those by the Office International des Epizooties [OIE]) are considered correctly. RTI conducted a formal and independent peer review as per the charge prepared by APHIS and conforming to OMB's guidelines for peer review and quality of information (OMB, 2002, 2004).

2 Description of the Risk Assessment

The risk assessment evaluates the risk of BSE introduction and establishment in the United States as a result of importation of certain commodities from a BSE minimal risk region (Canada). The commodities analyzed in the risk assessment are those that can be safely traded under certain conditions as per the OIE guidelines. Specifically, 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.

The analysis uses the approach recommended by the OIE 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 exposure. The analysis uses both qualitative and quantitative methods for various parts of the assessment such as prevalence estimation and exposure assessment.

To determine BSE prevalence in Canada, APHIS used quantitative models to estimate the present prevalence of BSE in the standing cattle population of Canada. However, these models cannot predict future changes in prevalence, which is necessary for 20-year time horizon considered in this risk assessment. Therefore, APHIS relied on qualitative evidence to evaluate the likely possibilities of how the prevalence may change in the future. Based on evidence from the United Kingdom (UK) and Europe about the effects of a feed ban, the

most likely possibility is that the prevalence will decrease continuously over the next several years. However, to evaluate an alternative (worst case) scenario for a quantitative analysis, APHIS assumed that the 2005 prevalence estimation remains constant for the 20-year analysis period instead of decreasing over the years.

For the exposure assessment model, APHIS used an extensively peer-reviewed model originally developed at the Harvard Center for Risk Analysis. APHIS modified the model and input parameters to more accurately reflect current regulations and industry practices. The qualitative analysis includes the assessment of the possible consequences of exposure that are not possible to predict by a quantitative model.

The final aspect of the assessment is the overall estimation of risk, which incorporates the results of the release assessment, exposure assessment, and the consequence assessment.

3 Description of the Review Process

RTI conducted the review process in accordance with OMB's guidelines (OMB, 2004). The review process consisted of selecting the reviewers, explaining the scope of the review, facilitating the review, and consolidating the reviews in a single report.

First, we selected four peer reviewers based on their expertise. We specifically considered their level of expertise in (1) the science of BSE particularly related to animal health; (2) modeling and quantitative risk assessment; (3) use of risk assessment as applied to regulatory decision making; (4) international animal health standards, especially OIE; and (5) the risks of BSE from importation of animal products. We initially identified 11 potentially suitable reviewers after discussing the background and objectives of the peer review with FSIS and APHIS. Subsequently, we finalized the list to four reviewers based on their availability and the desired overlap of expertise in the above five areas of expertise. We also ensured that the reviewers had no conflict of interest with the analysis.

Second, we provided the main risk assessment report to the reviewers and explained the scope of the review in terms of the charge to the reviewers prepared by APHIS. To aid the review, we also provided reports on BSE prevalence estimation in Canada and the Harvard exposure assessment model component as background documents. The charge to the reviewers consisted of five broad questions, as described in Section 4.

Third, RTI communicated and clarified any questions the reviewers had about the scope of the review or the analysis

itself. We communicated the progress and status of the review to APHIS and FSIS regularly and ensured that the reviewers were meeting the objectives of the peer review. We also ensured that the reviewers described possible ways to address their concerns instead of only describing the concerns. On APHIS's behalf, we also sought clarification to help better understand some of the reviewers' comments.

Fourth, we forwarded relevant public comments to reviewers for their consideration in revising their review. The comments were forwarded exactly as received by aphis, with attribution and no text redacted. We clarified to the reviewers that it was not their duty to refute any of the public comments. The main purpose of sharing the public comments was to aid reviewers in identifying any issue they might have missed while reviewing the risk assessment. Three reviewers noted that the public comments did not raise any issue that they needed to consider in their review explicitly. One reviewer discussed a few relevant public comments in his review. We removed any identification of the comment submitter from the reviewers report and instead referred to these comments as public comments 1, 2 or 3. The reviewer's discussion of the comments otherwise remain intact. We refer readers to Section 6, Review D for this discussion.

Finally, we consolidated the four reviews in this report. We provide brief background information on the four reviewers and include their peer reviews in Section 6.

To maintain the integrity of the reviews, we present the individual reviews as separate sub-sections in this report instead of consolidating the comments by the charge questions. Although we introduce the reviewers in Section 5, the individual review chapters are anonymous so that the peer review reflects the views of the panel and not of individual reviewers. Each reviewer focused on different aspects of the charge questions depending on his area of expertise, and their reporting formats and writing styles also differ. Therefore, reading each review separately can help readers better understand their comments. We have corrected minor typographical errors and reformatted their reports to ensure a minimum level of uniformity of presentation in this report.

4 Charge to the Peer Reviewers

APHIS asked the reviewers to focus their review on the specific questions listed below. We reproduce the charge to the reviewers below.

> The U.S. Department of Agriculture thanks you for agreeing to review this risk assessment. We are asking for you to review the overall assessment (including attachments and appendices) and also to address the specific technical questions as outlined below. As noted in recent OMB guidelines, peer review is an important process that helps to ensure that the quality of scientific information meets the standards of the technical community. Peer review also helps strengthen and clarify the risk assessment. Peer review should focus on the scientific aspects of the risk assessment and not on policy judgments based on the assessment.
>
> Toward the end of the review period, you will receive copies of public comments submitted through the rulemaking process that are applicable to the risk assessment. These are for consideration in your analysis and review as you deem appropriate.
>
> As you review the risk assessment, please structure your written responses to address the following:
>
> 1. General items:
>   (a) Does the analysis clearly convey the expected risk (including how this estimate was generated) of establishment of BSE in the United States as a result

of the proposed imports of live bovines and bovine products?

(b) Does the analysis adequately incorporate uncertainty and variability in the appropriate parameters in order to characterize the range of plausible scenarios (quantitative and qualitative) and their respective outcomes?

(c) Are significant sources of uncertainty clearly identified?

2. Use of available evidence:

(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.

(b) Does the analysis accurately characterize the cited literature?

3. Please examine the following assumptions used in the risk assessment and evaluate the extent to which these assumptions are reasonable and adequately supported:

(a) Qualitative assumption that BSE prevalence in Canada will decrease over the next 20 years until the disease is eradicated

(b) The import projections for live bovines from Canada over the 20 years of the analysis

(c) The assumptions related to the assessment of risk from the importation of bovine blood and blood products

    i. Assumptions regarding the localization of infectivity in various blood fractions

    ii. Applicability of non-bovine species data

For those assumptions or parameters listed above that you believe are not adequately supported or reasonable, please provide your recommendations for better supporting them, or your preferred alternatives. In the latter case, please include reasoning and evidence to support the new assumptions or parameters and comment on how these changes might have an important impact on the conclusions of the analysis.

4. Review the use of quantitative models in the release and exposure sections of the document, specifically the exposure simulation model and the prevalence

estimation methods. Please limit the discussion to those assumptions and parameters that have been applied to this assessment (and not already used in earlier versions of models that have been modified and incorporated into the current analysis). Specifically, for the various sections listed below, address the following:

(a) Were the quantitative methodologies used in this assessment applied appropriately to achieve the objectives of the release and exposure assessments?

(b) Review the following updates made to the models and changes to the input parameters as described, and evaluate whether the assumptions used to make these changes are reasonable and adequately supported. For those assumptions that you believe need revision, please justify the need for such revision and comment on why such changes might have an important impact on the conclusions of the analysis.

i. Qualitative and quantitative assumptions and parameters utilized in the live animal release section that are unique to the current analysis:

a. Assumptions regarding the age structure and stratification of the Canadian cattle population
b. Exclusion of negative surveillance observations for Canadian cattle imported into the U.S.
c. Exclusion of negative observations associated with epidemiological investigations of BSE cases in Canada
d. Use of diagnostic criteria applied to surveillance records for the identification of clinical suspects
e. In light of absence of statistical differences across birth cohorts, calculation of a single BSE prevalence estimate for the entire Canadian cattle population

ii. Quantitative assumptions and parameters utilized in the live animal exposure section that are unique to the current analysis:

a. Parameters and assumptions associated with the incorporation of the poultry litter feeding pathway
b. Updated parameter estimates for:
   § 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

5. Please comment on the degree to which the risk
assessment is consistent with international standards
and guidelines. The most relevant standards are those
promulgated by the World Animal Health Organization
(OIE). These are contained in the Terrestrial animal
Health Code, 14th ed. (2005): Chapter 1.3 (Risk
Analysis); Chapter 2.3.13 (Bovine Spongiform
Encephalopathy); and Appendix 3.8.4 (Surveillance for
bovine spongiform encephalopathy). (Available
at.http://www.oie.int/eng/normes/mcode/en_sommaire.
htm

5 Peer Reviewers

Below we list and provide brief biographical information on the reviewers in alphabetical order. We attach the four peer reviewer reports that we received from the reviewers in Section 6. These reports are randomly ordered, and they need not correspond to the listing of reviewers. We chose to keep the reviewers' individual comments anonymous so that all peer review reports are attributed to the group of four reviewers.

Ian Gardner, MPVM, PhD
Professor of Epidemiology, School of Veterinary Medicine, University of California, Davis

Dr. Ian Gardner is a Professor of Epidemiology in the School of Veterinary Medicine at the University of California, Davis. His main expertise is in analytic epidemiology, and his research interests include diagnostic test evaluation, risk analysis for livestock diseases and food safety, development of methods for certification of pathogen freedom in animal populations, and the epidemiology and transmission of Johne's disease in cattle. Part of his collaborative research with Dr. Wes Johnson involves application of Bayesian methods to diagnostic testing, prevalence estimation, and surveillance problems for animal diseases. He is an author of more than 200 peer-reviewed publications and has served on many national and international committees, panels, and review teams.

John B. Kaneene, DVM, MPH, PhD, FAES
University Distinguished Professor of Epidemiology and Director, Center for Comparative Epidemiology, Michigan State University

Dr. Kaneene is a University Distinguished Professor of Epidemiology at Michigan State University. Dr. Kaneene's research emphasis includes the epidemiology and mechanisms of antibiotic resistance, surface water contamination, bovine tuberculosis, and disease surveillance. He focuses on the epidemiology of foodborne pathogens and their relationship to the development of antimicrobial drug resistance in animal and human populations, particularly Campylobacter, Salmonella, and E. coli. He is actively involved in epidemiological studies and risk assessments of bovine tuberculosis in wildlife, livestock, and pets. He is conducting a comparative risk assessment of the introduction of avian influenza into the US and East Africa, from other regions of the world currently affected by avian influenza. As director and founder of the Center for Comparative Epidemiology (previously called the Population Medicine Center), Dr. Kaneene addresses issues involving epidemiology, preventative medicine, and public health on a variety of diseases.

Larry G. Paisley, DVM, MS, PhD
Senior Researcher, Department of Epidemiology and Risk Assessment, Danish Institute for Food and Veterinary Research, Denmark

Dr. Paisley, a Montana native, is currently a Senior Researcher at the National Veterinary Institute, Technical University of Denmark, Copenhagen, Denmark. Dr. Paisley received a DVM from Washington State University, an MS in theriogenology from the University of Minnesota, and a PhD in epidemiology from the Royal Veterinary and Agricultural University, Copenhagen. Denmark.

Dr. Paisley spent his early career as a therigenologist, teaching at Washington State University, Pullman, and Washington and Ross University; Basseterre, St. Kitts, W.I.

Since receiving his PhD in 1991 from the Royal Veterinary and Agricultural University, Copenhagen, Denmark, Dr. Paisley has worked for APHIS, USDA in Puerto Rico as an Area Epidemiologist and at Albany, New York, as the Northern Regional Epidemiologist. In 1996, Dr. Paisley began working at the National Veterinary Institute, Oslo, Norway, as an epidemiologist/risk analyst and in January 2000 began working at the Danish Institute for Food and Veterinary Research as an epidemiologist who focuses on TSE surveillance, disease modeling, and risk assessments. Dr. Paisley has conducted numerous TSE/BSE-related risk assessments for the Danish Veterinary Authorities, the Plant Directorate and Foreign Ministry. He participates in several EU-funded projects on TSE/BSE, FMD, CSF, and aquatic animal risk assessments and has been an invited expert on European Food Safety Authority (EFSA) Working Groups related to TSE quantitative risk assessments.

M.D. Salman, BVMS, MPVM, PhD, DACVPM, F.A.C.E.
Professor of Veterinary Epidemiology, Animal Population Health Institute, College of
Veterinary Medicine and Biomedical Sciences, Colorado State University

Dr. Salman is a Professor and Director of the Animal Population Health Institute of the College of Veterinary Medicine and Biomedical Sciences at Colorado State University. He holds appointments in the Department of Environmental Health and the Department of Clinical Science. Dr. Salman's educational background is in veterinary medicine, preventive veterinary medicine, and comparative pathology. His veterinary degree is from University of Baghdad—Iraq, and he received his MPVM and PhD from the University of California at Davis.

He is the author of over 180 refereed papers in scientific journals. He has participated in numerous conferences and national and international meetings in over 25 years as a faculty member. He has served on the board of scientific journals (Journal of Preventive Veterinary Medicine and the American Journal of Veterinary Research), and he is the section editor for the epidemiology section of Animal Health Review. He serves on several national and international professional and scientific committees in the animal health sectors. He was the chairman of the U.S. Animal Health Committee on Foreign and Emerging Diseases. He is engaged in research and outreach projects in more than 15 countries across the world. Dr. Salman holds a position on the peer review of the European Union scientific review for the geographical assessment for BSE. Recently he was elected to be on the European Food Safety Agency's Panel for Animal Health and Welfare. Dr. Salman is the chairman of the Continuing Education Committee of the Association for Veterinary Epidemiology and Preventive Medicine (AVEPM).

Dr. Salman's research interests are on the methodology of surveillance and survey for animal diseases with an emphasis on infectious diseases. He has published as the editor of a book entitled Animal Disease Surveillance and Survey Systems: Methods and Applications.

6 Reviews

We have numbered individual peer review reports as A, B, C, and D for ease of reference. RTI has formatted all reviews so all of the individual reports have a reasonably consistent format. We moved any references the reviewers cited to Section 7 of this report. The extent for the changes we made is strictly limited to changing fonts, bullet types, and paragraph properties.

To improve readability across the reviews, we number reviewers' comments as they correspond to the charge question numbers. For example, comments in response to Charge # 3 Question b sub-question i are reported under the heading CHARGE 3.a.i. Sometimes reviewers responded to only, say, Charge 4 in general and not to any sub-questions in particular. We organize such comments under heading CHARGE 4.

Review A

Introduction

I have been commissioned by the Food and Agricultural Policy program (FAPR) at Research Triangle Institute (RTI), to conduct a peer review of "Assessment of Bovine Spongiform Encephalopathy (BSE) risks associated with the importation of certain commodities from BSE minimal risk regions (Canada)" prepared by USDA: APHIS: VS dated October 27, 2006. The objective of the peer review is to confirm that the risk assessment is accurate, complete and transparent, the applications of external assessments or models are correct, whether the assumptions are justified, and if international standards (e.g., OIE) are considered correctly.

I have reviewed the Primary Document, Attachment 1. Estimate of the BSE prevalence in Canada and Attachment 2. The Harvard model component that addresses the exposure and consequence assessments provided by RTI as well as many other sources to arrive at my conclusions.

"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) (APHIS, 2006a)."

General Comments

In general, I found the report and supporting documents clearly written and relatively easy to understand. The report is transparent in regard to the assumptions and other input parameters. The use of both qualitative and quantitative methods in the same assessment was an interesting and justifiable approach. As will been seen later in this review, there are some issues that I believe should be revisited for possible corrections or revisions. However, most of these issues may not have a large effect on any of the conclusions reached in the report but might make the report more user friendly. Some of these are:

§   Listing of the specific risk(s) to be addressed in the assessment.

§   Listing of major sources of uncertainty

§   Description of the effects on uncertainties on model outputs and conclusions.

Overall Conclusion

The assessment suggests that importation, from Canada, of live bovines born after March 1, 1999, bovine blood and blood products and bovine small intestine excluding the distal ileum under the conditions specified present a negligible risk of establishment of BSE in the U.S

cattle population. Given the evidence presented, especially that in the exposure assessment, this conclusion appears to be justified.

CHARGE 1.a

The analysis, in general, does systematically convey expected BSE risks associated with importation of certain live bovines and bovine products in a well-documented fashion. However, I did not easily find where the exact risk question(s) to be answered was/were stated or what specific risks were being assessed. For example, the risk of establishment of BSE in the U.S. in Charge 1 is first mentioned in passing under Consequence Assessment. Not knowing in advance what the most important "endpoint(s)" made the task of reviewing the assessment more difficult.

It would also have been very useful if APHIS had included the criteria for a country to be classified as a Minimal Risk Region. For example, I had a difficult time understanding how the Canadian feed ban was considered effective as of March 1, 1999 when BSE cases were born in 2000 and 2002 until I read the "Final Rule: bovine spongiform encephalopathy; minimal-risk regions and importation of commodities" (APHIS, 2005). I interpret the rule to mean that a country must demonstrate that a feed ban has been implemented and rigorously enforced for a period of time but it is not necessary to show that it, indeed, is working. Thus, explaining the apparent tolerance for BSE cases born after the ban.

The assessment addresses the BSE risks associated with the importation of:

§ Live cattle born on or after March 1, 1999,

§ Blood and blood products,

§ Bovine small intestine,

In this case it would be helpful to identify early in the document what specific BSE risk(s) are to be addressed. Risk of importing an infected animal? Risk of clinical BSE in an imported animal? Risk of a BSE test positive imported animal? Risk of establishment of BSE in U.S. cattle? All of the above?

Apparently, the risk of greatest concern is the risk of establishment of BSE in the U.S. cattle herd as result of importation of live cattle and bovine products. The report begins with hazard identification, which in this case, is the agent that causes BSE. The next part of the report is made up of a release assessment, which describes the pathways necessary for an importation from Canada to 'release' the BSE agent into the USA as well as the probability that release will occur. Following the release assessment is an exposure assessment, which involves describing the biological pathways necessary to cause exposure of animals in the U.S. to BSE infectivity via Canadian imports well as the probability that exposure will occur. The consequence assessment describes the relationship between exposure to BSE infectivity and the consequences of the exposure. In this case, the adverse consequence of interest is the infection of U.S. cattle with BSE and the subsequent establishment of BSE within the national herd along with the associated probability of occurrence. Finally, risk estimation is

conducted, whereby the results of the release assessment, exposure assessment and consequence assessment are combined to produce an overall measure of risk.

Release Assessment

The main elements of the Release Assessment involve:

§   Estimation of the BSE prevalence in Canada

§   Release of infectivity by the aforementioned commodities

The prevalence in Canada was estimated by two different but correlated methods. The BSurvE Model and a Bayesian Birth Cohort (BBC) model that utilizes information about the Canadian feed ban. This methodology has been used previously in a published and peer reviewed document (APHIS, 2006b). BSE mean prevalence estimates for Canada from the BSurvE model ($3.9*10^{-6}$) (95th percent confidence level, $0.68*10^{-6}$) and the BBC model ($0.68*10^{-6}$) (95th percent confidence level, $1.1*10^{-6}$) as were reported and used to estimate the number of BSE infected animals that likely would be imported from Canada in 2007. Although the methodology used for the prevalence estimation for Canada was the same as that used for the U.S. (APHIS, 2006b), 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).

Regarding the release of infectivity by the imported commodities, APHIS presents evidence "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." Most of the evidence presented concerns the estimated low prevalence of BSE in Canada and the effectiveness of the Canadian feed ban and the probable associated decline in new BSE infections in Canadian cattle. See discussion of BSE prevalence estimates.

Regarding the release of BSE infectivity via blood or blood products APHIS concludes, "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" (APHIS, 2006a). This conclusion appears to be justified by the evidence presented.

Regarding the release of BSE infectivity via importation of bovine intestines APHIS concludes "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" (APHIS, 2006a). This conclusion appears to be justified.

In addition APHIS estimates the number of BSE infected cattle that would be imported to the USA from Canada in 2007 based on historical data on numbers and types cattle

imported in the past and the estimates of the BSE prevalence in Canadian cattle. Mean prevalence estimates from the BSurvE model ($3.9*10^{-6}$) and the BBC model ($0.68*10^{-6}$) resulted in the estimated importation (in 2007) of 5.37 or 0.94 BSE infected cattle, respectively. It is expected that these numbers will decrease in the future as a result of the Canadian feed ban. The upper 95% confidence limits for these estimates were not addressed in the release assessment conclusion.

<u>Conclusions of the Release Assessment:</u> "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" (APHIS, 2006A).

> <u>Comment</u>
>
> Based on the evidence presented this conclusion may be justified. However a qualifying statement addressing the amount of uncertainty associated with the conclusion is needed. For example the 95th percent confidence "levels" should also be reported and used throughout the assessment. This may change the conclusions. The conclusion appears to be justified in the case of blood, blood products and distal ileum and if only the BBC prevalence estimate is used. However, I question 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. I do not believe that the results of the BSurvE model and the 95th percent confidence "levels" of either model should be ignored or under emphasized.

Exposure Assessment

The Harvard BSE model was adapted and revised to fit this specific assessment. The model simulates the impact of various scenarios and mitigations on the likelihood of BSE infection, spread, establishment in the U.S. given BSE infectivity was imported with live bovines or bovine products. The initiating step in the pathway is the importation of ca. 1.3 million bovines from Canada assuming for the base case that the BSE prevalence is $0.68*10^{-6}$ in 2007 (The expected value for BSE prevalence from the BBC model). It assumed that the prevalence remains stable at that level over the next 20 years, a very pessimistic assumption. The model evaluates the effects of:

§ SRM removal efficacy

§ Proportion of cattle rendered

§ Mislabeling and cross-contamination at rendering plants and feed mills

§ MBM disposition

§ Misfeeding

In addition to the base case scenario, sensitivity analysis was conducted such that pessimistic values (i.e., expected value for BSE prevalence from the BSurvE model) were

substituted for the base case values and the effect of these substitutions on the outputs were reported.

Conclusions of the Exposure Assessment:

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, R0, that predict that any imported infectivity will ultimately disappear from the population" (APHIS, 2006A).

> Comment: It is very reassuring that even with the pessimistic assumptions regarding BSE prevalence in Canada and effectiveness of mitigating measures the R0 remained below 1 indicating that BSE will not become established in the US cattle population. It would be informative if R0 would remain below 1 if the simulation were done using the 95th percent confidence limit for the BSE prevalence obtained with the BSurvE model.

Qualitative exposure assessment for blood and blood products: "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" (APHIS, 2006A).

Qualitative exposure assessment for importation of bovine small intestine other than the distal ileum: "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" (APHIS, 2006A).

> Comments
>
> The conclusions reached in the exposure assessment appear to be justified. It was prudent not to attempt to predict the future decline in the Canadian BSE prevalence in that even the base case results were bad, if not worst, case scenarios. It was also comforting to see that even with the pessimistic scenarios explored in the Sensitivity analysis the R0 remained at less than 1 suggesting eventual die-out of BSE even if US cattle were exposed to BSE infectivity from Canadian imports. This section suggests that even if concerns regarding the estimates of the current BSE prevalence in Canada are well founded, BSE is not likely to be established in the US via imports from Canada. However, I believe that the exposure simulations should also have been done using the 95th percent confidence limits of the BBC and/or the BSurvE models as inputs. If R0 still remains below 1, the conclusion would have more credibility.

Regarding the conclusion 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" is likely true. However, a statement regarding any uncertainty about the conclusion would be desirable.

Regarding the conclusion that "exposure of US cattle to BSE in bovine small intestine imported from Canada is extremely unlikely" is also likely true (APHIS, 2006A). However, a statement regarding any uncertainty about the conclusion would be desirable.

Consequence Assessment

The consequence assessment addresses the unfavorable impact(s) should BSE infected animals or products be imported to the US from Canada. The consequences requiring consideration are economic and environmental. Because the impacts to the human environment are covered by a different risk assessment only the economic impact was considered.

Conclusions of the consequence assessment: "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" (APHIS, 2006A).

Comments

It seems that the consequence assessment, while likely correct, is somewhat superficial given the gravity of BSE. The consequences of importing of BSE infected cattle or cattle products would be very different depending on which segment of the cattle industry or population was affected. For example, importing infected cattle destined for slaughter would not likely have a great consequence whereas importation of infected cattle for breeding or milk production may have severe consequences in herds that import them. It is far more likely that a BSE infected animal imported from Canada if not slaughtered a young age will become a clinical or rapid test positive case than to become a source of exposure for the US cattle population. Any new BSE case will result economic costs, some short term, some long term. However, APHIS presents arguments, based on past experience and new agreements with trading partners, suggesting any economic cost due to new cases (to the nation) will be minor. However, the authors acknowledge that the market impact of a new BSE case or cases is difficult to predict. Given, the evidence presented in this assessment it is likely that very few or no BSE cases will occur as a result of imports of cattle and cattle products from Canada.

Risk Estimation

Risk estimation combines the results of the release assessment, exposure assessment and consequence assessment to produce an overall measure of risk.

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" (APHIS, 2006A).

> Comments

> If the endpoint of the risk assessment is the establishment of BSE in the US cattle population, given the apparent low BSE prevalence presently in Canada, the likelihood that it will continue to decrease and the mitigating factors in force, this conclusion appears to be justified.

CHARGE 1.b

It seems to this reviewer that a lot of effort was expended to incorporate uncertainty and variability in the parameters but that the uncertainty in the qualitative outcomes was not fully acknowledged. Perhaps, it is just a matter of style, but given the uncertainties associated with many of the parameters, some conclusions seem to be presented with more conviction than they deserve.

The major source of uncertainty and variability are the estimates of the BSE prevalence in Canada. Contributing to this parameter uncertainty are uncertainty regarding the age structure of the Canadian cattle population, the "effectiveness" of the Canadian feed ban, when the Canadian ban became "effective," the appropriateness of the default exit constants used in the BSurvE model, assignment of BSE tested cattle to the clinical suspect category and age distribution of BSE tested animals. Each of these points is discussed in the main risk assessment document and in Attachment 1: Estimation of BSE prevalence in Canada.

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. The BBC uses the surveillance points for cohorts generated by the BSurvE model that have associated uncertainty and combines this information with an assumed reduction in BSE infections due to a feed ban that became effective at an assumed date (March 1, 1999)—more uncertainty.

The validity of these both of the assumptions can be questioned in light of the fact that three (possibly four) of the Canadian BSE cases were born after March 1, 1999 when the feed ban was supposed to be fully implemented and enforced (CFIA, 2006). 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 the decline in the incidence of BSE incidence following the MBM ban in Canada may or may not be the same as seen in the UK following its first feed ban. This uncertain!

The fact that three different but related methods were used to estimate the BSE prevalence demonstrates that there is considerable uncertainty regarding the prevalence. Although the expected value (mean) and the 95th percent confidence level for the prevalence calculation by the BBC and BSurvE models are shown in Table 3, pg 25 only the lower mean (expected) values are used or mentioned in the rest of the release assessment. This down plays uncertainty. It is also unclear what the " 95th percent confidence level" represents, especially when referring to the Bayesian Cohort model. It appears to me that these should be the "upper 95% confidence interval limits." In addition, in contrast to classical statistics that compute "confidence intervals," Bayesian statistics compute "credible intervals" or "Bayesian confidence intervals." The two are not strictly comparable.

Because the "95th percent confidence levels" were computed and presented in table 4, I believe that the values should also be used in the other calculations, simulations and conclusions. This would better address the uncertainty.

It 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.

Other important sources of parameter uncertainty include: mislabeling and contamination rates, misfeeding rate, reduction in infectivity by rendering, and the proportion of poultry litter used in feed. These issues are well addressed in section IV.A.2.b.2 Sensitivity Analysis Results.

CHARGE 1.c

It would, perhaps, be useful to actually list the sources of uncertainty in each of the sections.

In my opinion uncertainty is consistently underplayed if not ignored. It is readily apparent in the discussions that the authors are aware of the uncertainties in many of the parameters. However, when stating the conclusions uncertainty, generally, is not mentioned.

The word "uncertainty" only appears nine times in the main document. Of the nine, five address uncertainty in the Canadian BSE prevalence estimates. These prevalence estimates were identified as the most important exogenous source of uncertainty but the sources of that uncertainty were not specifically identified. Further, in the release assessment it

appears that only the mean prevalence estimate of the BBC model was used to form the conclusion that the likelihood of importing BSE infected cattle from Canada was extremely low. The mean (expected) prevalence from the BSurvE model as well as the 95th percent confidence levels for both models were not mentioned.

The other uses of "uncertainty" were the percentage of cattle dying on the farm that are rendered, the misfeeding rate, extent of the use of poultry litter in cattle feed, cross contamination and mislabeling. These were part of the Exposure Assessment.

Although other many sources of uncertainty are alluded to and discussed at length in the risk assessment and supporting documents in very few instances they are actually identified as sources of uncertainty.

In contrast to the rest of the report, the Executive Summary is written in manner such that the reviewer is clearly aware that there is considerable uncertainty and what was done to address the uncertainty.

CHARGE 2.a

The references appear to be adequate. However, It should be noted 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, Berinque 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).

Arnold and Wilesmith (2004) support the assumption that most BSE infections occur in the first year of life.

CHARGE 2.b

Not always. For example, in paragraph 2 page 15 the authors cite a study by Ferguson et al. 1997 as a source suggesting that most cattle are exposed to BSE infectivity and become infected in the first year of life. Ferguson et al. (1997) states that the "peak (of infection) occurs at one year of age, not at birth" (pp. 814). If one looks at the probability distribution it can be seen that the majority of infections occur at greater than one year of age in this model.

In the same paragraph the statement "Specifically, the simulation estimates that susceptibility declines exponentially after the age of 4 months leveling off at 10% of the peak value" (De Koeijer et al., 2004)" is not strictly correct. "Susceptibility declines exponentially after the age of 4 months leveling off at 10% of the peak value" was an assumption used when calculating the R0 for BSE. In addition, this is not a simulation model.

CHARGE 3.a

Because of the implementation of the Canadian feed ban in 1997, the further strengthening during the years until July, 2007 when all specified risk material (SRM) will be prohibited in animal feeds, pet foods and fertilizer this assumption appears to be justified.

CHARGE 3.b

The projections have been made by the 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. The projections seem reasonable.

CHARGE 3.c.i

The assumptions appear to be justified primarily because BSE infectivity has not been demonstrated in bovine blood.

CHARGE 3.c.ii

I believe that in this case the application of non-bovine species data is justified in this case given: "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." I have found no place where this information if used would greatly influence the risk estimate.

CHARGE 4.a

The quantitative methodologies used in this assessment include:

§   Estimation of the BSE prevalence in Canada with the:

–   BSurvE model

–   BBC model

§   Estimation of the number of BSE infected animals imported in 2007 based on the prevalence estimates generated by the BSurvE and BBC models and the estimated numbers and types of imported cattle.

These methodologies have been discussed in the section on Release assessment. Given the caveats pointed out previously, the methods have been applied appropriately.

§   Quantitative evaluation of the BSE exposure and spread in the United States

The quantitative evaluation of the BSE exposure and spread in the United States was done with a modified and updated version of the Harvard BSE model (Cohen et al., 2001, 2003). The current model differs from previous versions in that instead on a single importation of

BSE infected cattle in the previous versions multiple importations of different age, type, sex etc. can be accommodated. In addition, potential exposure of cattle to the BSE agent via consumption of poultry litter can be assessed. Other input parameter estimates were updated including:

§ 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

The original Harvard model and revisions have been published, have undergone peer review and have been deemed appropriate to evaluate BSE exposure and spread in the United States thus it can be assumed that the revised, updated model presented in this analysis is appropriate if the revisions and updates are appropriate.

CHARGE 4.b.i.a

Age specific mortality and slaughter rates for are unavailable for the Canadian cattle population so cattle population demographics for the US (as estimated in the Harvard model of Cohen et al., 2003) were applied to the Canadian cattle population data derived from cattle inventory data by Statistics Canada (http://www.StatCan.ca). If the estimated US cattle population demographics are reasonable then their use for the Canadian population is acceptable. It appears that this is the best information available. This, however, is a source of uncertainty.

CHARGE 4.b.i.b

The reason that this was done is clearly explained and justified. Its effect is to slightly inflate BSE prevalence estimate for Canada.

CHARGE 4.b.i.c

The reason that this was done is clearly explained and justified.

CHARGE 4.b.i.d

The reason that this was done is clearly explained and justified.

CHARGE 4.b.i.e

The reason that this was done is clearly explained and justified.

<u>CHARGE 4.b.ii.a</u>

This potential pathway is new to the Harvard model. The authors assume that 50% of prohibited MBM goes to feed mills producing prohibited feeds (excluding poultry feed); 5% of prohibited MBM goes to mixed feed mills and the remaining 40% goes to poultry feed mills. They further estimate that on average, 1% of poultry litter nationwide will be used in cattle feed and assume that 100% of any infectivity that may be in poultry feed goes to the litter. The final assumption is highly pessimistic. The other assumptions seem justified.

<u>CHARGE 4.b.ii.b</u>

§ Efficacy of SRM removal at slaughter: Assumed that SRM is removed effectively 99% of the time. No change from previous models.

§ Proportion of animals that are rendered: 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% with an upper bound of 42% (FDA, 2005a, page 58588). The current analysis assumes the higher value of 42% to reflect those cattle dying on farm that are rendered. This parameter value is lower, however, than the 85% assumed in previous analyses (Cohen et al., 2001, 2003). The change appears justified.

§ Mislabeling and cross-contamination at rendering: FDA/CVM compliance data (prior to September 2003) indicate that mislabeling was detected in 2.3% of inspected renderers and possible commingling (cross-contamination) was detected in 1.8% of inspected renderers. The model uses these values to indicate the relative likelihoods of these nodes within the risk pathway. The authors suggest that compliance has likely improved since then. These values appear to be justified although maybe pessimistic.

§ Mislabeling and cross-contamination at feed mills: 2002 FDA feed ban compliance data (FDA, 2002) report that 4% of prohibited feed is mislabeled, and 1.9% of prohibited feed cross-contaminates non-prohibited feed. These values are lower than in previous models but higher than those suggested by more recent compliance data so would tend to overestimate the cross-contamination and mislabeling occurring now. These assumptions are valid.

§ Disposition of MBM: In previous models the authors assumed that 15%-30% of MBM produced in the US was exported whereas in 2004 the actual amount was five percent. In addition, the proportion of MBM used in poultry feed needed to be specified. The new values and the values in older models are shown in Table 8. The new values appear to be reasonable assumptions.

§ Pessimistic value of misfeeding for sensitivity analysis: The base case scenario in previous models assumed that 1.6% of correctly labeled prohibited feed is

misfed to cattle and a pessimistic value of 30%. Based on data from the National Grain and Feed Association and the American Feed Industry Association the pessimistic value was lowered from 30 to five percent. This change appears to be justified.

CHARGE 5

The analysis was conducted following the guidelines of the World Organization for Animal Health (OIE, 2006). The import risk analysis process begins with hazard identification, which involves identifying the pathogenic agents that potentially could produce adverse consequences associated with importation of a commodity (OIE, 2006). In this case, the hazard is the agent that causes BSE. The associated commodities are those listed above. The adverse consequence is the establishment of BSE in the US national cattle herd. Hazard identification is followed by release assessment. Release assessment involves describing the pathways necessary for an importation to 'release' the hazard into the environment of interest (USA) as well as the probability that release will occur. Exposure assessment follows release assessment. Exposure assessment involves describing the biological pathways necessary to cause exposure of animals in the importing country (USA) to the hazard as well as the probability that exposure will occur. Consequence assessment describes the relationship between exposure to the hazard(s) and the consequences of the exposure. In this case, the adverse consequence of interest is the infection of US cattle with BSE and the subsequent establishment of BSE within the national herd as a direct result of the importations along with associated probability of occurrence. Finally, risk estimation is conducted, whereby the results of the release assessment, exposure assessment and consequence assessment are combined to produce an overall measure of risk.

In my opinion, the risk assessment is consistent with the standards and guidelines of the OIE.

Review B

CHARGE 1

This risk assessment clearly details the expected risk, and rigorously describes how estimates of risk were generated, for establishment of BSE in the U.S. as a result of importation of live bovines and bovine products from Canada. The Executive Summary provides a good overview of the process used by the authors. The final assessments, that the risk of release and exposure of BSE via live cattle is negligible as the prevalence of BSE declines in Canadian cattle, and that risks for BSE via blood and blood products, and small intestine other than the distal ileum are unlikely, are clearly presented in the executive summary and conclusion of the report. The authors concisely define the scope of their risk assessment, which was limited to animal health pathways and consequences, and to the risks associated only with imported bovines and bovine products (not including any potential risk from indigenous cases of BSE in the U.S.). They also provided detailed information into the current BSE outbreak in Canada, including methods used in surveillance and disease detection, and the governmental programs established to eradicate BSE from the country.

Using guidelines established by the O.I.E. for risk analysis in the Terrestrial Animal Health code, the authors conducted hazard identification for BSE in bovines and bovine products. The authors provided thorough literature reviews of the epidemiological and experimental studies currently available that addressed issues in the transmission, incubation, tissue distribution and relative infectivity of different tissues in cattle that were pertinent to their risk assessment. This research has focused on the BSE situation in cattle in the UK, and some studies of disease pathogenesis in laboratory animals, and the authors have appropriately applied this information to both qualitative and quantitative analyses. This process allowed the authors to classify risk into three categories, based on the type of import: live bovines, blood and blood products, and small intestine other than the distal ileum.

Within each category of import, the authors then generated a release assessment, and provided extensive documentation and justification for estimates of the prevalence of BSE in Canada, the infectivity of live bovines, blood and blood products, and small intestine other than the distal ileum, and projections of future imports being brought into the U.S. from Canada. The release assessment for the importation of live bovines from Canada into the U.S. examined the prevalence of BSE in Canada, and steps taken by Canada to eradicate BSE from their cattle population. Examination of steps taken to eradicate BSE included a discussion of the feed ban in Canada, especially at how well the ban was implemented, and the current risks posed by BSE-contaminated feeds in Canada. The discussion on issues associated with contaminating ruminant feeds with potentially infective ruminant tissues were discussed, including risks of cross-contamination or mislabeling products at feed mills processing both ruminant and non-ruminant feeds. The authors also discussed the

importance of education for affected stakeholders, and emphasized how education was critical to improve compliance with regulations designed to eradicate BSE.

One component critical to the release assessment for risk associated with the importation of live cattle was determination of the prevalence of BSE in Canadian bovines, particularly for use in the exposure assessment portion of the risk analysis. Simulation models, based the "BSurvE" model for the relative likelihood of detecting BSE in various strata of cattle (based on age and causes of death), were used to estimate the prevalence of BSE in the Canadian bovine population given the results of current surveillance programs, and estimates of the population profile of Canadian cattle based on the U.S. cattle population. An extension of this model, including information from the UK experience with BSE following a ban on feeding ruminants material likely to contain BSE and implementing Bayesian analyses, was developed to provide estimates of prevalence more appropriate to the Canadian BSE experience. The use of Bayesian methods in this newer model, the Bayesian Birth Cohort (BBC) model, allowed the authors to structure variability into their model. The assumptions for both models were clearly described in the text, providing descriptions of how estimates were generated, and frank discussions of the weaknesses of some of these assumptions. However, given the lack of available information required for parameterization of these models (e.g., population profiles of Canadian cattle), and assuming that feeding bans in Canada prove to be as effective in reducing BSE as did bans in the U.K., the authors provided reasonable arguments for the assumptions used in their approach.

Next, an exposure assessment was conducted, starting with a pathway analysis to describe the barriers to BSE transmission and amplification in the U.S. for each type of import. The pathway analysis drew heavily from the hazard assessment and release assessment, and neatly expressed how existing safeguards in the U.S. would decrease the likelihood of spreading any BSE imported into the country. Next, simulation modelling and sensitivity analysis were conducted for the quantitative evaluation of BSE exposure and spread, based on results of the release assessment for BSE transmission from importing live bovines from Canada into the U.S., and mitigated by the control strategies described in the pathway analysis. A thorough description of the modelling process was provided, and clearly identified the modifications made in the current models in comparison to the previous versions of the simulation developed jointly by the Harvard Center for Risk analysis and Tuskegee University. The changes to the model were well-organized, and clearly explained the rationale behind new parameter estimates. Qualitative assessments for BSE exposure and spread were conducted for bovine blood and blood products, and small intestine other than the distal ileum, and pathways and assumptions were described in detail. Again, given limited information in these areas, the assumptions used in the analysis were appropriate.

The authors also conducted a consequence assessment to describe expected economic impacts of BSE cases emerging in the U.S. While brief, the assessment discussed major issues arising from BSE on export markets, consumer responses, and institutional costs associated with surveillance and eradication of BSE. The authors acknowledged the difficulties inherent in attempting to predict the multi-faceted economic consequences of

cattle disease and do not attempt to make specific dollar estimates, but manage to make a reasoned estimation of the impact of BSE in the U.S. beef industry.

CHARGE 2

The analysis appears to have used relevant peer-reviewed studies, and the authors have appropriately interpreted the findings of the published studies.

CHARGE 3

All risk assessment requires a variety of assumptions for parameterization of risk models, and the authors provided a thorough explanation of the rationale behind the assumptions used in their models. 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. Assumptions regarding import projections for the next 20 years appeared to rely on current import estimates. However, 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. Despite the variability of findings in the infectivity of different tissues and blood fractions, and the differences seen in different species, the assumptions related to the risk from processed blood products appears to be valid given available research.

CHARGE 4

The quantitative models applied to the release assessments were appropriately defined and utilized, as described in the authors' detailed description of the modeling and parameter estimation processes. Presenting the modifications made to the models, with documentation for the rationale behind the changes, into separate sections made the changes to the model easy to identify and comprehend. Since no data were available on the age structure and stratification of the Canadian cattle population, and given the high similarity between the U.S. and Canadian livestock industry and populations, using U.S. estimates for the age structure and stratification of Canadian cattle was valid. Since the prevalence estimation modelling was based on surveillance data within Canada, exclusion of negative surveillance observations for Canadian cattle exported to the U.S. was appropriate. Including the positive Canadian import cases found in the U.S. did inflate the numbers of cases observed through surveillance, it allowed the process to ultimately provide more

conservative estimations as to the efficiency of BSE reduction strategies by assuming possibly higher than actual BSE prevalence in the current Canadian cattle population. Observations from epidemiological studies were appropriately excluded, as they were not conducted under the same protocols as routine BSE surveillance, and hence were not comparable observations to those collected under normal surveillance. The diagnostic criteria for identifying cases of BSE from surveillance records was clearly described, and was appropriately applied.

Based on empirical evidence and results from the prevalence modelling of BSE in Canadian cattle, a single BSE prevalence estimate was applied to the entire cattle population, based on the absence of statistical differences across birth cohorts. The authors justified this by noting that animals born within two years of a case would have been exposed to similar risk (through feed contamination), and that the prevalence of BSE in cattle for up to 7 years prior to the birth of the case would have influenced the case by contributing infected tissue to the feed that served as the source of infection for the case. While the results of modelling support this contention, the biological reasons for maintaining a single prevalence value need to be explored further. The associations between case birth cohorts and those from years before (contributors to the case), and around (common risk of exposure) the case cohort, indicate that the prevalences were not independent, but did not indicate that prevalences should be identical. From a biological perspective, this is in disagreement with what is known about the exposures and risks of infection for different cohorts, particularly in light of the results of the feeding bans. The authors correctly noted that using a single prevalence estimate resulted in a conservative approach to the final risk assessment, and they interpreted their results with this in mind.

The parameterization of the live animal exposure model, and the underlying assumptions, were clearly presented and very appropriate. The incorporation of poultry litter as a potential source of infection was an interesting addition to the model. The parameter estimates associated with infected cattle products entering the feed production process were clearly presented and effectively justified. The use of pessimistic values for sensitivity analysis followed the authors' conservative approach for the risk assessment, and was accounted for in their interpretation of model results.

One general question that the models did not cover concerns those cattle/cattle products that were not exportable and were not rendered (i.e., farmer/rancher disposal): 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.

CHARGE 5

In conclusion, this was an excellent risk assessment for the introduction of BSE into the U.S. from imports of bovine commodities from Canada, and is consistent with OIE standards.

Review C

Introduction

The aim of this report to present the findings from a risk assessment study conducted to evaluate the potential BSE risk associated with the proposed regulations regarding the importation of animals and animal products from regions that present a minimal risk of introducing bovine spongiform encephalopathy (BSE) into the United States through live ruminants and ruminant products and byproducts. The study restricted this minimal risk region to a specific area in Canada. 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 specific conditions. The three commodities that are involved in this assessment are: 1) live bovines (cattle and bison) that were born after the date when a ruminant-to-ruminant feed ban was effectively enforced in Canada; 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 risk associated with these commodities and the likelihood that these products imported from 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 for trade-related animal health risk assessments.

I have reviewed this report. The report is well-structured and comprehensive in assessing the risk of introduction of the BSE agent through the importation of specific commodities from Canadian minimal risk regions. Below are my comments and suggestions:

CHARGE 1.a

The estimate of the expected risk, as a result of the proposed imports of live bovines and bovine products, was derived from sound assumptions and analysis of current available data and observations. Thus the conclusion from this report in terms of the expected risk is reliable given these assumptions and data.

CHARGE 1.b

The authors of this report have incorporated adequately the potential for uncertainty and variability in most parameters in order to characterize the range of plausible scenarios and their respective outcomes. However, some of the assumptions for the model are unclear. For example:

The 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.   The statement by the authors "as this model cannot predict future changes in prevalence, we qualitatively evaluate the available evidence to anticipate how the prevalence may change" is not clear in relation to the use of the quantitative model. I suggest presenting a flow chart with the various paths and the estimation of parameters for the quantitative model as it is considered the final model for the assessment.

The authors did not consider constant prevalence for their qualitative assumption. I suggest considering another scenario to incorporate the 20% drop within the next five years. The five year period is a proxy of the incubation period and beside it was the time interval that was used by the European GBR.

CHARGE 2

The authors have properly used available evidence from various sources. They have utilized approaches used in previous studies and assessments to support their findings.

CHARGE 3.b

I think it will be difficult to predict the flow of cattle from Canada to the USA for the next 20 years. This type of projection will depend on economic growth and weather conditions. Using retrospective data for this projection will not be sufficient unless a wide range of parameters can be used. I commend the authors for their attempts to utilize various parameters in order to derive the best estimates for the potential flow of cattle and bison between Canada and the USA.

CHARGE 3.c.i

I believe that the authors of this report have admirably attempted to utilize available information for assessing the potential spread of BSE through the importation of blood. The current proposed conditions for such imports have already considered all the precautions needed to avoid contamination of the imported blood.

CHARGE3.c.ii

The assessment of the importation of bovine small intestine, other than distal ileum, under certain conditions is less detailed and comprehensive as compared to live bovine and blood. I recognize the limitations in data related to this type of products. The authors may want to consider reviewing the use of this type of products and the likelihood for ruminates to be exposed to these products. I believe this type of exposure is rare if it does indeed exist.

CHARGE 4.a

The quantitative models used for the release and exposure components were well thought-out. The quantitative techniques used in this assessment were applied appropriately to achieve the objectives of the release and exposure assessments. I however, suggest including a simple flow chart of the pathways in order for the readers to understand the structure of the models.

CHARGE 4.b.i.b

I suggest incorporating the imperfection of the Canadian surveillance system with a much wider range as part of the sensitivity analysis for the entire assessment process.   I believe that neither the USA nor Canada has good monitoring system for compliance with the feed ban. Nevertheless the authors performed the best that can be done in this situation. I suggest including a statement to indicate the lack of sufficient compliance with the feed ban in both countries. I do not think the outcome from the presented risk assessment will be changed but it will satisfy our European counterparts.

CHARGE 4.b.ii.b

The authors attempted effectively to estimate parameters for the efficacy of SRM removal at slaughter and the proportion of animals that are rendered. The estimations of the cross-contamination at rendering and at feed mills are reasonable. The assumption of the disposition of MBM is not fully justifiable. The authors may want to consider further evidence for their assumption. I do not believe that all the SRM are removed. Furthermore, some of this SRM will reach the cattle feeding system but I believe that this amount is deserted by all means. Again it will be better to add such a sentence in the report to indicate that this issue was not neglected.

CHARGE 5

As I indicated above the authors have used the conventional risk assessment process that is suggested by international agencies. The process used by the authors followed the recommendation by the OIE Terrestrial animal Health Code, 14th ed. (2005): Chapter 1.3 (Risk Analysis); Chapter 2.3.13 (Bovine Spongiform Encephalopathy); and Appendix 3.8.4 (Surveillance for bovine spongiform encephalopathy).

In conclusion I feel the report has addressed and responded to the questions that this risk assessment process intended. As in any of this type of risk assessment the actual risk from this introduction is still uncertain but at least we know this level of risk will be negligible given the current knowledge and data.

Review D

Introduction

From a technical perspective, I believe that the BSE risk assessment is sound (see comments to specific charges below) and consistent with OIE guidelines.

The following points should be considered during revision of the document:

§   The BSE risk estimates should be updated to include the new Canadian case that was detected in February 2007.

§   The 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. Hence, a natural reaction of stakeholders might be to compare prevalence in the U.S to that in Canada. Because that is not the intention of this risk assessment, perhaps this should be explicitly stated in the Introduction section of the document.

§   Because 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 Ro is still less than 1, even in this extreme case.

§   The analysis indicates that Ro 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 Ro to approach 1, i.e., for BSE to cycle given the mitigations in place.

§   Time to eradication of BSE. One 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 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.

§   Geographic 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. The comment about spatial heterogeneity of BSE was also raised in one of the public comments (see my comments in section VI) and extended to include spatial heterogeneity in Ro values.

In my opinion, the presentation of the BSE risk assessment document was excellent because it combined writing in the active voice, it included an overview of what to expect in

the subsequent sections of the document and it had a very strong focus on biology, transmission and the relevant peer-reviewed literature. I found the arguments presented in the document well-motivated and supported by appropriate journal citations. I believe that the assumptions were clearly listed. The use of footnotes was a nice addition to provide additional details that would otherwise clutter the text. From my perspective, the only improvement in the presentation would have been to include one or two figures showing the scenario pathways for the undesired outcomes (perhaps with the mitigations shown). This would have made it easier to visualize which steps are in series and which are in parallel.

In sections II and III, I answer the specific charges to the reviewers, then make comments about the two attachments (Estimation of BSE prevalence in Canada and the Harvard model of BSE) and finally list some editorial suggestions and note some typographical errors that I found during the review. Finally in section IV, I conclude with comments on relevant section of the 3 public response documents that were forwarded by email on March 14, 2007.

CHARGE 1.a

Yes

CHARGE 1.b

Yes. The main source of variability incorporated into the analysis is via the prevalence estimate generated in the release assessment. In the BBC model, for example, temporal changes in prevalence after the feed ban are incorporated as well as time-dependent adjustment factors to account for exit from the Canadian cattle population. This variability is incorporated into the model supporting the exposure assessment for live bovines. However, I believe that it would be helpful to readers to have an explicit list of model inputs that are considered variable.

CHARGE 1.c

Yes

CHARGE 2.a

Yes. I found one reference – Bohning and Greiner (2006) – that was not included but is at least indirectly relevant to the statement on page 21 about including all cattle regardless of whether they are at a detectable stage of disease.

Additional references were also mentioned in the public comment documents. Ideally, an updated literature search should be done as part of the revision of the risk assessment document.

CHARGE 2.b

Yes, based on my knowledge of the subject matter area but I did not reread papers specifically for the purpose of this review.

CHARGE 3.a

Very reasonable, based on British experience. This opinion was not shared by all of the respondents in the public comments.

CHARGE 3.b

It is difficult to comment on this aspect because I am not an economist. However, I suggest 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?). In 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.

In addition, I 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.

CHARGE 3.c.i

Reasonable and well justified

CHARGE 3.c.ii

In the absence of bovine data, this is the next best alternative

CHARGE 4.a

Yes, appropriately used along with qualitative approaches

CHARGE 4.b.i.a

Reasonable

CHARGE 4.b.i.b

Reasonable. Choice of this approach means that prevalence would be slightly overestimated compared with the alternate approach.

CHARGE 4.b.i.c

Reasonable.   Choice of this approach means that prevalence would be slightly overestimated compared with the alternate approach.

CHARGE 4.b.i.d

Reasonable

CHARGE 4.b.i.e

Reasonable, but with so few total cases the statistical power to detect differences between cohorts is probably low. This point was also raised in the NCBA comments.

CHARGE 4.b.ii.a

Not able to comment on the relevance of this pathway

CHARGE 4.b.ii.b

All seemed reasonable and based on best available evidence

CHARGE 5

Very consistent. Also meets the criteria listed in a recent publication by Heim et al. (2006)

Other suggested modifications to the report:

Page 3 – add a conclusions section under B2 to be consistent with the prior section

Page 8 – clinical signs of any disease? – suggest be more explicit and say "clinical signs consistent with BSE", or similar

Page 15 – not exactly annual incidence since there is no denominator – better to say the "number of incident cases"

Page 19 – "100-fold more sensitive" (why, because much more tissue is used?)

Page 22 – not sure that the BBC method provides a more precise estimate, probably just more realistic

Page 24 – Exit constants should probably be explained in more detail in a footnote

Page 27 – In the paragraph before III.B.A.1.a, I think it would be helpful to add a transitional sentence or two along the lines of "In the following sections, we provide a detailed explanation for our choice of March 1, 1999 as the date the feed ban was effective.

This date allowed time for adequate implementation of the feed ban and for the ban to have its desired effect"

Page 51 – Prevalence not Prevalance

Page 57 – ...the Harvard model... cites evidence

Page 62 – I think it should be five (not six) uncertain parameters

Comments about relevant sections of the public comments

a.   Public Comment # 1

The comments regarding the risk assessment (on pages 4 to 6) are essentially those related to the prevalence of BSE in Canada and the importation of BSE animals from Canada. Regarding prevalence, the public comment # 1 contends that prevalence in Canada is about 7-fold higher than in the U.S. and that it cannot be established whether prevalence is decreasing, increasing or remaining static. The latter is a crude measure only since it is the birth-cohort specific incidence which is the most relevant parameter indicating whether the epidemic is under control or not. Given the rarity of the outcome, I doubt that there will be adequate statistical power to detect whether there is an increasing, static or decreasing trend. The public comment # 1 contends the resumption of bovine imports without restriction on the date of birth would be detrimental to the U.S (page 6, mid page). I am unclear as to the meaning of this statement since the date of birth must be later than the date when the feed ban was considered to be "effective" for purposes of risk modeling. This was estimated to be March 1, 1999, based on a 6-month phase-in period from August 4, 1997 plus an additional 12 months to exhaust on-farm supplies of prohibited material.

b.   Public Comment # 2

The public comment # 2 are well-articulated, constructive and supported by sound scientific and logical arguments. The public comment # 2 relate to the release assessment, the exposure assessment, and the date of the effective ban. The comments acknowledge the credibility and validity of the Canadian surveillance efforts, epidemiologic investigations, and efficacy of the feed ban. On pages 7-9, public comment # 2 lists a series of areas requiring clarification and further discussion. Points 1-6 relate primarily to the risk assessment, and 7-9 relate to rule implementation and economic impacts on the cattle industry. I found all the requests for clarification and discussion reasonable and hence, should all be responded to meaningfully.

c.   Public Comment # 3

This document is very detailed and relevant comments in the document with regard to the risk assessment are on pages 31 to 43 and 61 to 79.

An expert's comments attached to public comment # 3 include a series of bolded main points. The first relates to terminology in current use for risk assessments e.g. minimal risk,

negligible and effective. I concur with some of these especially in the use of the term "effective" which requires the specific outcome to be evaluated and modifier such as 100%, 95%, 50% etc. Within the first section (page 3), the expert estimates the prevalence of BSE as being much higher than those proposed by USDA. However, I do not agree with his methods of calculation of BSE prevalence. The methods of calculation used by APHIS are more realistic given the sampling design and the relative weighting factors. Regardless of the exact nature of the calculation, there is no disagreement as to the fact that BSE infected animals will likely be introduced into the U.S. over the 20-year period, as predicted by the Harvard model. The approach, correctly taken by APHIS, is how to manage those risks in an acceptable manner.

The expert raises a good point about the possible spatial heterogeneity in Ro values. That geographic clustering of cases occurs in Canada is undeniable given the evidence from epidemiologic investigations by CFIA. Even if cattle from these Canadian "hotspots" are introduced into the U.S, their distribution to slaughter plants and ranches will be unpredictable. Moreover, there is no indication that the mitigations in place in the U.S. are not effective. The calculation of activation of a "hotspot" in the U.S. on page 8 is somewhat simplistic. With this said, I think this point about spatial heterogeneity should be addressed in the response to public comments. In my original comments, I raised the possibility of zoning as an option and recommend that specific comments be made about this as a possible risk management option.

Other comments/Corrections to the attachments to the main report

Attachment 1: Estimation of BSE prevalence in Canada

Page 4 – fourth last line "data are.."

Page 14 – a minor point but the statement "converging to local rather than global maxima" is not really correct. This implies convergence to a number – the convergence is to a distribution.

Page 16, second last line – the Bayesian analysis, it is really a probability interval rather than a confidence interval. Regardless, it might be clearer to describe these as "confidence limits".

Page 17, table 5 – is it the 95th percentile or the 97.5th percentile in the Bayesian analysis?

Page 17, second line beneath the table - "uncertainty and not variability". One 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.

Pages 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.

Attachment 2: Harvard model of BSE

Page 25: I did not receive appendix 2B for review. However, this appendix was offered to aid my review by RTI. After considering that fact that this was a large file (> 5 Mb) with figures and that this information was not critical to address the charge to the reviewers, I declined the offer to review this document at a later time.

Page 26, line 4 – perhaps add the following in parenthesis after "infected animals" (existing and newly infected) for clarity

Appendix 2A, section 2.6 – mean column: 5.8E172 and 5.8E174. Please make this easier to read for clarity.

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