Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States

Response to Reviewer Comments submitted by Research Triangle Institute
(RTI project number 07182.024), October 31, 2002

Joshua T. Cohen
George M. Gray

Harvard Center for Risk Analysis
Harvard School of Public Health

October, 2003

We appreciate the comments USDA has solicited in response to our report evaluating the potential risk of BSE if it were to be introduced into the United States, as presented in the Research Triangle Institute report dated October 31, 2002 (hereafter referred to as "RTI"). We welcome the opportunity to make use of these comments to strengthen the report. While this memo does not aim to address all the reviewer comments point by point, we hope that it can help clear up what we believe were some misunderstandings about the purpose of our analysis and some of the assumptions made. Although the responses are deliberately terse we mean no disrespect to the reviewers or their efforts in reviewing the report.

To this end, we have grouped our responses into the following sections:

- I. Purpose of Analysis: This section explains why we did not extensively analyze various potential scenarios for the introduction of BSE into the U.S.
- II. Alternative Assumptions: We recognize that there are different possible interpretations of the literature and available data, as identified by the reviewers. We have quantitatively evaluated some of these suggestions by running new simulations and have addressed other suggestions qualitatively. As explained below, we do not believe the comments cast doubt on the overall conclusions reached in our analysis.
- III. Specific Responses: After these general comments, we offer brief responses directly addressing specific reviewer comments. We describe modifications made to the original report release (November, 2001) that appear in the revised report (October, 2003).

I. Purpose of Analysis

The reviewers claim in a number of places that the Harvard – Tuskeegee (H-T) report fails to adequately address potentially important scenarios by which the BSE infective agent (hereafter referred to as "infectivity") might be introduced into the U.S. These scenarios include, for example, bioterrorism (RTI, p. 2-5) or the import of contaminated feedstuffs (RTI, p. 3-4).

As explained in this section of our comments, estimating the likelihood of such scenarios was outside the scope of our report. Instead, our purpose was for the most part to evaluate what might happen if such an introduction occurred. A key purpose of the model is to serve as a tool to evaluate different actions that can be taken to manage risk. For example, the report states in Section 1 that, "… *the analysis describes the use of a quantitative simulation model that*

characterizes how the introduction of BSE would affect animal health over time, and the extent to which it could result in human exposure to contaminated food products" (line 477). Hence, we did not attempt to quantify the probability that BSE might have been introduced in the past (with the exception of our analysis of cattle imported from the UK during the 1980s), nor did we attempt to estimate the probability that it might be introduced in the future. Section 1 of the report continues, stating, "*… we do not quantify the probability that BSE will be introduced into the U.S. Hence, all our risk estimates are conditional on hypothetical scenarios.*" (line 507). For this reason the H-T report states in its introduction that "*The analysis is not a complete human health risk assessment…*" (line 504).

The purpose of our study must be kept in mind when interpreting our results. For example, the statement in the Executive Summary of the report that, "*Our analysis finds that the U.S. is highly resistant to any introduction of BSE…*" (line 332) does <u>not</u> mean that we believe the introduction of BSE into the U.S. is necessarily unlikely. We did not evaluate this probability. What the statement does mean is that if BSE were introduced into the U.S., we found it is highly unlikely that it would spread extensively. That is, we believe that the prevalence of the disease would generally decrease over time after its introduction, rather than increase, as it did in the UK in the 1980s. For these reasons, a distinction must be made between review comments suggesting that our introduction scenarios underestimated risk (*i.e.*, the probability that BSE might be introduced into the U.S.) and comments suggesting that other aspects of our model underestimate risk. The former are outside the scope of our analysis.

Our purpose also explains why we did not need to model all means by which BSE might be introduced into the U.S., such as bioterrorism or (in the November, 2001 report version) the import of contaminated feedstuffs. The scenarios we did consider can be thought of as a proxy for other introduction scenarios. In the case of scenarios involving a one-time introduction or a limited number of introductions (*e.g.*, bioterrorism), our scenarios that consider the import of up to 500 infected cattle can be considered to be a proxy because in all cases, such introductions result in the initial seeding of the simulation with a certain number of infected animals. How the animals became infected (*e.g.*, they were infected before they were imported into the U.S., they were infected by the import of contaminated feed, *etc.*) does not matter. What our simulation results show is that in all cases (up to at least 500 infected cattle), BSE prevalence tends to decrease over time. As the assumed initial number of infected cattle increases, the time it takes for the disease to become eradicated increases. There is no reason to believe this property does

not hold when the number of cattle initially infected increases. For periodic introductions of infectivity, our scrapie scenario serves as a useful proxy. The model could easily be used to investigate what might happen if the rate at which infectivity was periodically introduced were increased. The October, 2003 report includes an additional introduction scenario that models the import of BSE-contaminated cattle feed.

We also note that while we did not explicitly investigate all possible means by which infectivity might be introduced into the U.S., our approach did make it necessary to consider all plausible means by which such infectivity might be recirculated. For this reason, we explicitly modeled the possibility of maternal transmission of BSE to calves.

II. Alternative Assumptions

As is true in the case of many risk problems, it is difficult to identify sources of data that can be used to quantify model parameters. This difficulty was exacerbated in the case of BSE by the fact that much of the critical data and information that have been gathered are not available in the open literature, but are instead available only in unpublished reports or as expert judgment. Although we attempted to identify all available literature through extensive interaction with experts in both Europe and the U.S., we recognized that there were still substantial gaps in the understanding and quantification of factors that influence the extent to which this disease spreads.

Our general approach in the November, 2001 report to address this limitation was to conduct a non-parametric univariate uncertainty analysis that quantified the extent to which variation in each parameter over the full range of plausible values influences key estimates computed by the simulation model. That report found that only a small number of parameters have a non-trivial impact on either the expected (arithmetic mean) number of infected cattle or potential human exposure to BSE infectivity. In response to reviewer comments, we extended the analysis to consider all of the model's parameters. Note that our consideration of all of the parameters in the model does not mean that we used the simulation model to quantify the impact of alternative values in all cases. As explained in the October, 2003 report, we were able to dismiss the need to quantitatively evaluate many of these parameters on qualitative grounds. Nor have we investigated all of the alternatives suggested by the reviewers.

First, in many cases, the reviewers do not provide any indication as to why they expect that a suggested change might have a substantial influence on the results. In these cases, we are left with the option of either running an additional sensitivity analysis for the many possibilities they have raised, or constructing an argument for why the parameter may be important and then offering a counter argument. For example, the reviewers ask (RTI, p. 2-4), "*For instance, what effect would reducing the number of age categories have on the results? Or what effect would varying the accuracy (decimal places) of blood meal consumption have on the results?*" The reviewers do not explain why changing the number of decimal places should be expected to have a substantial impact on the results. Given the size of this model, evaluating these and other similar possibilities could go on almost indefinitely.

Second, in many other cases, the reviewers have suggested that alternative values for various parameters would be more defensible but do not identify either documentation or even what values they believe we should have used. For example, the reviewers criticize our assumed ante mortem inspection BSE detection rate. They state, "*Also, with respect to recognition rate (where only the very typical cases will be recognized), it is assumed that 90 percent (in the case of worst case, 50 percent) of the BSE clinical cases will be detected in the ante-mortem inspection, which is way off from the general feeling in the EU on this topic*" (RTI, p. 9-5). What alternative value should we use and based on what reference? In any case, as Figure 4-1 in the October, 2003 H-T report indicates, this parameter has only a tiny impact on the expected number of infected animals. Figure 4-3 in the October, 2003 H-T report indicates that its impact on estimated human exposure is likewise small.

The reviewers correctly noted that our November, 2001 report did not directly quantify potential synergistic effects among uncertain quantities (RTI, p 2-4). That is, we did not, for example, determine what would happen if two parameters were simultaneously assigned their worst-case values. The importance of simultaneously evaluating the impact of multiple worst case assumptions is limited in the case of this simulation because only a very small number of parameters were at all substantially influential and because the two most influential parameters we did identify (*i.e.*, feed mislabeling probability or misfeed rate – see Figures 4-1 and 4-3 in the October, 2003 H-T report) are unlikely to be correlated. As a result, the possibility that the true value of both of these influential parameters are equal to their respective worst-case values is small. Nonetheless, in response to reviewer comments, the October, 2003 report version does investigate the impact of simultaneously assigning worst case values to multiple parameters.

Finally, we appreciate the comments on model parsimony. However, because the model's development was aimed in part at developing a tool for risk management, its complexity must be sufficient to investigate the effectiveness of potential mitigation strategies. For example, our in depth treatment of CNS tissue emboli formed in stunning is necessary to evaluate the effect of changes in risk management options under consideration.

III. Specific Responses

The section numbers below correspond to the section designations in the R-T report.

2 General Comments

2.1 Overall Strengths of the Model

No specific response.

2.2 Overall Weaknesses of the Model

- Paragraph 1 does not identify a specific assumption that, if changed, would have a substantial impact on the results.
- Paragraph 2 – See our comments on purpose of analysis (Section I, above).
- Paragraph 3 – We do not understand the claim that we do not need the model to predict that the risk for BSE is low. How do we know *ex ante* that an epidemic would not occur if BSE were introduced in the future? In addition, without the model it is not possible to quantitatively evaluate the effect of alternative risk management strategies.

2.3 Clarity of Model Structure

- Comments (1) and (2) – The discrete event simulation is described in sufficient detail for the reader to understand the basic relationships and assumptions. Moreover, the exact values for all parameters are specified. Ultimately, with a model of this complexity, it is necessary to review the computer code itself to precisely understand the relationships. This code will be made available to the general public. The documented source code has been made available to another party reviewing the H-T report (the Swiss Federal Veterinary Office) at their request.

2.4 Complexity and Level of Detail

- Comment (1) – Paragraph 1 – The model's complexity is necessitated by several factors. First, the system simulated exhibits positive feedback. Second, factors influencing the spread of disease (*e.g.*, MBM consumption rate and infection susceptibility) are correlated and can change substantially over a short time scale on the order of months. The reviewers do not indicate what aspects of the model they believe could be eliminated and why.

- Comment (1) – Paragraph 1 – The sensitivity of the model to different parameter values has been addressed by our sensitivity analysis.

- Comment (1) – Paragraph 1 – The reviewers do not state which parameters are characterized in too little detail. For the parameters mentioned, they do not explain why changing the level of detail might substantially affect our results. As noted earlier, this detail may be necessary to support the evaluation of specific risk management strategies.

- Comment (1) – Paragraph 2 – What level of detail is correct for the natural death rate? As it stands, the H-T simulation assumes a total of seven different rates. What is the advantage of collapsing this rate down into, for example, one category?

- Comment (1) – Paragraph 3 – We have included vertical transmission because the available evidence suggests that it is plausible. If anything, our inclusion of this pathway makes the model results more pessimistic. Hence, eliminating this pathway would not affect our qualitative conclusion that the U.S. agricultural system is robust against the introduction of BSE. In any case, this pathway is responsible for only a modest number of the BSE transmissions in the base case (0.63 out of 3.6, on average).

- Comment (1) – Paragraph 4 – See our general comments on sensitivity analysis (Section II, above).

- Comment (1) – Paragraph 5 – Age, type, and gender influence MBM exposure and the slaughter rate. Any correlation between exposure and slaughter rate can affect the point in the incubation period when an animal is culled and hence the amount of infectivity that might be recycled.

2.5 Omission of Exposure Routes

- Comment (1) – Segments of the U.S. that behave essentially as relatively isolated agricultural systems with their own characteristics (*e.g.*, greater use of rendering technology that is less effective and neutralizing the BSE agent) could be more susceptible to the spread of BSE, such regions exist. Although the simulation model could be used to investigate this issue, characterizing such segments of the U.S. agricultural system was beyond the scope of this project.

- Comment (2) – See our general comment on purpose of analysis (Section I, above).

- Comment (3) – The October, 2003 report evaluates the impact of importing contaminated feed. See also our general comment regarding the purpose of the analysis (Section I, above).

- Comment (4) – The possibility that BSE might be present in muscle tissue would not "*dramatically alter the structure of the model and the risk estimates*" (RTI, p. 2-6). The materializer parameter file allows the user to specify what fraction of carcass infectivity exists in each tissue, including muscle. The possibility that a substantial amount of BSE is in muscle tissue is unlikely. The Scientific Steering Committee of the EU evaluated the study on prions in mice and issued the following statement: ***"****Given the limited conditions of the research reported on and the consistent negative results of infectivity experiments with regard to the presence of TSE infectivity in muscles of cattle and sheep, there is currently no reason to revise the SSC opinions with regard to the safety of bovine and sheep muscles. Also, should infectivity be present at very low levels below current detection limits, the risk of exposure to BSE infectivity is reduced to negligible levels by risk reduction measures in place and by the fact that exposure would be via the relatively inefficient oral route*." This evidence indicates that at worst, the disease process deposits very little BSE infectivity in muscle tissue. Given that we already recognize the possibility that muscle tissue will become contaminated with BSE during the slaughter process, it is hard to imagine how our results would be noticeably influenced by the assumption that BSE may be present in muscle before slaughter.

- Comment (5) – The October, 2003 report evaluates the impact of importing contaminated feed. See also our general comment regarding the purpose of the analysis (Section I, above).

2.6 Presentation of Model Outputs

- We have created a table based on the reviewer's recommendation (see Appendix 3D).

2.7 A Basic Aspect of BSE

- See our general comment on purpose of analysis (Section I, above).

2.8 Treatment of Literature and Expert Knowledge

- Comment (1) – This particular comment does not identify any specific omissions from the report.

- Comment (2) – The October, 2003 report explains that we used our own judgment to interpret the implications of the existing literature on BSE.

3 Identification of Data and Critical Evaluation of Evidence

3.1 Have All Key Studies and Data Been Identified?

We note that the reviewers did not identify any data that would change any assumptions or results.

- Comment (1) – Paragraph 1 – We have fixed the missing references.
- Comment (1) – Paragraph 2 – It is not clear what the comment is referring to. What kind of table and where should it be inserted?
- Comment (2) – The study mentioned refers to scrapie, not BSE. The pathogenesis study found no detectable levels of BSE infectivity in muscle, which indicates that at most, the levels would have to be very small. Finally, it does not appear that some BSE in muscle would substantially affect the results. At most, it would moderately increase potential human exposure to the infective agent, with the magnitude dependent on how much BSE (cattle oral ID_{50}s) is in muscle.
- Comment (3) – A regulation banning the rendering of cattle on the farm has <u>not</u> been introduced. It is a hypothetical measure that we evaluate.
- Comment (4) – The first bullet does not call for a response or action. Regarding the second bullet, there is no additional information that is publicly available.
- Comment (5) – References have been added.
- Comment (6) – This particular comment does not specifically identify any material that we should reference. However, see also our response to Comment (23) in Section 3.2.
- Comment (7) – The paper by Scheuder is referenced in the first paragraph of Section 2.4.3. The paper by Hörnlimann is not referenced because it is in German.
- Comment (8) – Paragraph 1 – Appendix 1, Section 3.17 specifies the exact incubation period distribution used. Paragraph 2 – See our general comments on purpose of the analysis (Section I, above).

3.2 Have the Data Been Correctly Interpreted and Emphasized

- Comment (1) – The specifics pertaining to this general comment appear in subsequent comments and are addressed below.

- Comment (2) – The reviewers identify two "optimistic" assumptions that they claim "*cannot be verified with confidence*" (RTI, p. 3-4). We recognize that these assumptions are very uncertain. However, the report does document both the development of the assumed implementation rates for the feed ban (Section 4.3 in Appendix 2) and the assumed amount of infectivity that may have been introduced into the U.S. from the UK during the 1980s (Appendix 4). The reviewers do not explain what aspects of those derivations they believe to be insufficient.

- Comment (3) – See our general comments on purpose of the analysis (Section I, above).

- Comment (4) – The statement is based on USDA's records for the imported animals. The reviewer states that some statements are "questionable" but does not say which ones and does not offer alternative assumptions.

- Comment (5) – The reviewer does not offer any citation to support his claim that the two log reduction for rendering with added fat is optimistic. This assumption is based on data from Taylor, *et al.* (1995) Veterinary Record **137**:605-610

- Comment (6) – We do not understand this comment. What is meant by the statement that "*the model is based on unlikely events such as air-injected stunning*" (RTI, p. 3-5)? Why would this make the model limited or obsolete? As explained in the report, we included the ability to model air-injection pneumatic stunning so that it would be possible to evaluate past practices and possible future changes in those practices.

- Comment (7) – The quotation is taken out of context. It is based on the detection rate computed by USDA and the analysis based on the results illustrated in Figure 4-7 in H-T.

- Comment (8) – We do not understand this comment or what its implications are for our model.

- Comment (9) – This comment may be correct. However, the reviewers do not describe how the ProbPassAM parameter should be modified. Moreover, the sensitivity analysis indicates that the model's results are insensitive to this parameter.

- Comment (10) – The absolute magnitude of the population does not affect the simulation. As explained in the report, the relative magnitude of each population group (*i.e.*, each group of cattle with the same age, gender, and type) influences exposure because it influences the probability that recycled feed will be sent to each group. This point is now addressed in Section 3.2.1.1 of the October, 2003 report. Although using any population size that preserves the relative size of the different groups would work, it is easiest to use a population size that comes

close to the actual population size. This reviewer also notes that the H-T model does not account for potential variation by season or by geographic region. We did not model seasonal changes because it is unlikely to have a substantial impact on the simulation's results. Instead, we used values averaged over all seasons. We agree that geographic variation can be important if there are some regions that have both a large number of animals that pose a larger than typical risk and practices that increase this risk. The H-T model could be used to investigate risks in such sub-regions, although doing so was beyond the scope of the H-T report.

- Comment (11) – The relationship noted in the comment is described in Section 3.1.1.4 of the H-T report.

- Comment (12) – The "≥" should not be in this table. The simulation parameter files reflect the assumption that the incubation period cannot exceed the value of 130 months. Because the probability mass beyond this point is so small, it is unlikely that this truncation has had any important impact on the results.

- Comment (13) – We do not know what this comment refers to.

- Comment (14) – Section 3.1.3.3 describes how the parameter is used. Its correct value, which was used in the simulation, is 89 (the value of 88 specified in the November, 2001 report was a typographical error).

- Comment (15) – The revised report addresses a range of scenarios, including the import of live cattle infected with BSE and the import of BSE-contaminated feed. We do not understand the reviewer's suggestion that we address a scenario in which "*an internal processing system that is incapable of reducing infectivity below a certain threshold level (mainly the rendering system)…*" For example, the base case scenario assumes that 5% of all animals are rendered by systems that do not reduce infectivity levels at all.

  This comment also says that the H-T report should have addressed the potential import of infected animals from Mexico and Canada. As the commenter notes, the H-T report describes why the prevalence of BSE in either Canada or Mexico would not be very high (notwithstanding the recent discovery of a BSE case in Canada). Hence, even though the number of cattle that enter the U.S. from Canada and Mexico is substantial, the number of infected animals would remain very small. Our simulation evaluates the import of up to 500 infected animals into the U.S. and therefore addresses the possibility raised by the reviewer.

- Comment (16) – The reviewer does not provide any citations for the claim that the exported animals had a greater risk than the remainder of the cohort. Nor does the reviewer specify the magnitude of this difference. As a result, we do not know how we should revise our analysis based on this comment.

- Comment (17) – The reviewer does not suggest a specific change to the text and does not provide any references to support the comment made.

- Comment (18) – The suggested text has been inserted.

- Comment (19) – It is not clear how the reviewer would suggest the susceptibility distribution be modified. However, this point is important, and clarification would be useful. We note that the October, 2003 report has added a sensitivity analysis to evaluate the implications of assuming that susceptibility decreases more slowly than we have hypothesized in our base case.

  We also note that the distribution used in the model (H-T Figure 3-4) is consistent with the statements on p. 3-12 of RTI that, "*If there is an age-dependent susceptibility it is not absolute. That is, all ages are susceptible.*", and "*The epidemiological evidence from the epidemic in Great Britain is that age at exposure does not influence the incubation period.*" We do not understand the last paragraph of this comment or how the reviewer proposes we modify our assumptions (or even which assumptions he is proposing that we modify here).

- Comment (20) – We have been unable to locate the paper referred to in the comment as "Kinberlin (1997)". Nor can we find any reference to the "EU-sponsored Great Britain exercise." We have therefore not revised the text referred to in this comment.

- Comment (21) – The reviewer does not explain why the first sentence in Section 2.2.2 of H-T internally inconsistent? It is possible for a disease to be both rare and to be long-established (*i.e.*, to have been around for a long time). We note the comment on the relative age of cattle in the UK *vs.* other European countries.

- Comment (22) – We believe it is worthwhile to briefly discuss each hypothesis. Many are dismissed through references to SEAC or SSC.

- Comment (23) – We have added text language at line 1370 ("*Experience in the UK during the BSE outbreak, when swine had significant exposure to BSE contaminated feed, suggests that the disease did not cross the species barrier to infect pigs.*") and cited http://www.defra.gov.uk/animalh/bse/bse-science/level-4-transmis.html#species to support the hypothesis that pigs do not harbor infectivity.

  The last paragraph in this comment states that the report should have referred to absolute numbers of pigs slaughtered before the age of six months, rather than to the corresponding percentage. We have not revised this text. The report refers to the proportion of pigs (rather than absolute numbers) to support our point that even if a porcine TSE existed, the probability would be small that substantial infectivity would develop in any given pig prior to slaughter. Moreover, as the report notes (paragraph starting at line 1387), there are a substantial number of pigs that live beyond the age when clinical signs would be apparent. The fact that none has ever shown such signs casts doubt on the existence of a TSE in pigs.

- Comment (24), paragraph 1 – The October, 2003 report now includes text that refers to scrapie research as the source of information used to identify tissues that harbor high levels of infectivity at line 1652 ("*This legislation banned from the animal feed chain tissues identified as potentially harboring the highest concentration of infectivity. This determination was made based on knowledge of the distribution of infectivity in animals infected with scrapie.*").

Comment (24), paragraph 2 – We have added the following text at line 1663, which provides a complete list of the SBO – "*During the first few years following the initial identification of BSE in Britain, the epidemic was primarily an animal health concern. That focus reflected the experience with scrapie, which despite its presence in the human food supply for hundreds of years, had never lead to a known case of human illness. There was some concern given knowledge of the ability of scrapie to cross species under certain circumstances. Precautionary measures were nonetheless put into place to protect the human food supply, including a ban on the sale of brain, spinal cord, spleen, thymus, tonsils and intestines from cattle older than 6 months (materials designated as specified bovine offal or SBO) for human consumption.*"

Comment (24), paragraph 3 – The discussion of the CJD surveillance unit has been corrected and a citation added (see paragraph starting at line 1672).

Comment (24), paragraph 4 – We have added text to address this comment at line 1697 – "*SEAC recommended in March, 1996 that carcasses from cattle aged over 30 months be deboned and all obvious lymphatic and nervous tissue be removed in licensed plants and that the trimmings be classified as SBO. For practical reasons, instead all animals greater than 30 months of age were prohibited for human consumption. When the pathogenesis study suggested potential BSE infectivity in dorsal root ganglic, a ban on sale so of bone-in-beef was introduced.*"

- Comment (25) – This section does not attempt to "evaluate" BSE surveillance in the U.S., something that is outside the scope of this document because surveillance does not directly influence the spread of the disease.

3.3 Are All Input Data Used in the Model Valid and Appropriate?

- Comment (1) – This response addresses specific examples referred to in this general comment where they are detailed in the reviewer comments.

- Comment (2) – The availability of the source code should clear up any questions that are not directly addressed by the report text.

- Comment (3) – We did not use continuous distributions to describe uncertain assumption parameters because we judged the information available to be inadequate to assign relative probabilities to alternative values. See the paragraph starting at line 2551.

- Comment (4) – See our general comment on alternative assumptions (Section II, above) and our discussion of the use of sensitivity analysis. The reviewer does not explain why the two examples noted in this comment would be at all likely to substantially influence the results of the simulation.

- Comment (5) – Regarding the comment on Felidae and ungulates, we have added the following text at line 545, "*TSEs have also been observed in exotic cats and ungulates in zoo collections. The source of infection is not known.*" Regarding

Kuru, the text now reads (line 559), "*Kuru is characterized by neurologic signs and neuropathologic changes similar to those of scrapie although it has other signs (e.g., myoclonus) not seen in scrapie but found in other TSEs.*"

- Comment (6) – No citation is provided.

- Comment (7) – The text has been modified so that it reads (line 1575), "*In countries with BSE, one common risk management strategy is the removal of infected tissues from the human food supply or animal feed.*"

- Comment (8) – Noted. The October, 2003 report evaluates the impact of altering these assumptions (see report Sections 3.2.1.4 and 3.2.1.6). The results indicate that neither of these assumptions have an important influence.

- Comment (9) – This typographical error has been corrected in the October, 2003 report. This error did not affect the parameter file used in the November, 2001 report.

- Comment (10) – To evaluate the potential impact of changing the age at import, we reran the simulation of the import of 500 infected cattle assuming that these cattle were infected at the age of 4 months rather than at the age of 12 months. Changing the assumptions as suggested had only a small impact on the results, including the number of newly infected animals (mean increase from 220 to 270 animals), the probability that BSE will remain in the U.S. after 20 years (increase from 11% to 14%), and human exposure (no change in mean exposure).

- Comment (11) – The surveillance referred to here reflects the screening of animals judged by USDA to have an elevated risk of being infected with BSE. These animals include "*cattle exhibiting signs of neurologic disease, cattle condemned at slaughter for neurologic reasons, rabies-negative cattle submitted to public health laboratories, neurologic cases submitted to veterinary diagnostic laboratories and teaching hospitals, and sampling of cattle that are nonambulatory ('downer cattle'/fallen stock)*" (U.S. Department of Agriculture (2002). *Bovine Spongiform Encephalopathy: Surveillance*. Animal and Plant Health Inspection Services. Accessed: 2003. Available at: http://www.aphis.usda.gov/lpa/issues/bse/bse-surveillance.html.) We cite the publicly available information on USDA's surveillance program.

- Comment (12) – The reviewer does not provide an alternative for our assumption that there were four undetected animals with BSE in the UK for every one that was identified. Nor does the reviewer indicate that a more realistic assumption would substantially affect the calculation. For the last part of this comment, see our response to Comment (16) of Section 3.2 (above).

- Comment (13) – See Section 4.3 of Appendix 2 in the October, 2003 report.

- Comment (14 – Noted. However, we were unable to identify any more specific data and the reviewer does not offer any specific citation.

4 Overarching Logical Structure of the Risk Assessment

- Comment (1) – Comment does not call for a response.

- Comment (2) – The reviewer refers to simulation as a suboptimal approach but does not offer an alternative. We used simulation modeling rather than statistical modeling because there are no empirical data that can be used to develop a model of what would happen if BSE were introduced into the U.S. Nor can a statistical model always be used to test the influence of potential risk management options.

- Comment (3) – Although the comment explains why the GBR approach overstates risk, it does not explain why the H-T study might underestimate risk.

- Comment (4) – While the figures suggested by the reviewer have some favorable characteristics, we believe our illustrations are more helpful because they more directly correspond to the structure of the model we developed.

- Comment (5) – The reviewer claims that "*the processes involved from the birth of an animal to its death and ultimately the fate of it remain unanswered*" (RTI, p. 4-2) We do not understand what processes the reviewer is referring to. The report specifies the birth rate for all animal types and both the natural death and slaughter rates for all animals by type, age, and gender.

- Comment (6) – Paragraph 1 – The reviewer suggests that instead of estimating the probability that prohibited feed is fed to cattle that we instead estimate the probability that "a mistake is made". We do not understand this comment. The event we are interested in is the feeding of properly labeled prohibited feed to cattle.

- Comment (6) – Paragraph 2 – The suggestions in this paragraph are too vaguely specified for us to understand what the reviewer is suggesting and how we should modify our analysis.

- Comment (7) – The reviewer does not propose a specific revision.

- Comment (8) – The reviewer states that the model has not been fully validated. Not only do we agree with this statement, but we say so in both the November, 2001 version of the report and the October, 2003 version of the report. For example, we state (line 3641) that "*It is important to note that this is not a true validation and, in fact, the model's predictions could be close to reported observations for the 'wrong reasons'*".

5 Biological Plausibility of the Assumptions

- Comment (1) – Regarding the constant ratio assumption (for the UK imports scenario), see our response to comment (12) in Section 3.3. Regarding the assumption that imported animals were infected at the age of 12 months, see our response to comment (10) in Section 3.3.

- Comment (2) – First paragraph – we reran the base case simulation with the assumption that the amount of infectivity in an animal never falls below 256 ID_{50}s after the infectivity reaches that level in the distal ileum. The table below specifies the original assumption and new assumption for this parameter.

Months Since Infection	Total Infectivity in Carcass (ID_{50}s)	
	Original Assumption	**New Assumption**
0-1	0	0
1-5	8	8
6-18	256	256
19	0.03	256
20	0.07	256
21	0.15	256
22	0.31	256
23	0.64	256
24	1.35	256
25	2.83	256
26	5.95	256
27	12.51	256
28	26.29	256
29	55.24	256
30	116.09	256
31	243.97	256
32	512.71	512.71
33	1077.47	1077.47
34	2264.31	2264.31
35	4758.48	4758.48
36	10000	10000

The results revealed that this revision has only a small impact on the predicted number of newly infected animals (mean increase from 4.3 to 5.2), the probability that BSE remains in the U.S. after 20 years (decrease from 0.3% to 0.1%), and the predicted human exposure (mean increase from 39 to 51 ID_{50}s). Note that this alternative set of assumptions has been specified only for the purpose of determining if the qualitative point raised in the comment might have a substantive impact on our results. The points in paragraph 2 are noted. Note that the decrease in the probability that BSE will still be present in the U.S. after 20 years is the reverse of what would be expected, indicating that this difference represents stochastic noise.

- Comment (3) – We do not understand this comment.

- Comment (4) – The October, 2003 report evaluates the scenario in which contaminated feed enters the U.S. See also our general comment on scope of analysis (Section I, above).

6 Are the Mechanics of the Model Consistent with Known Biology?

- See our responses to comments in Section 11. In short, we believe the model has been extensively and clearly documented.

7 Appropriateness of Modeling Techniques (Model Mathematics and Equations)

- Comment (1) – Paragraph (1) – The reviewer states that "*there is no documentation of the analytical approach used in the model…*" (RTI, p. 7-1). We do not know what this comment means. Every parameter is completely documented. Section 3.1 steps through the events simulated in detail. Of course, the process we have simulated is complex, and that makes it difficult to take in. However, we do not know what specific information about the simulation the reviewer has been unable to find.

- Comment (1) – Paragraph (2) – The reviewers state that they were unable to "*find mathematical equations to describe the BSE simulation report…*" (RTI, p. 7-1). Although it is technically possible to describe any simulation as a series of equations, we chose not to use equations to describe our simulation because it represents a discrete event model. In these cases, describing what events occur provides a much clearer explanation than would a series of equations. In fact, we are aware of articles in the peer reviewed literature that do not use equations to describe discrete event simulation models (see *e.g.*, Roderick *et al.*, 2002, "The evaluation of screening policies for diabetic retinopathy using simulation," *Diabetic Medicine*, 19:762-770). Note that using equations to describe the Harvard BSE model would be far more complicated because the model tracks multiple objects (cattle, ID_{50}s) and collections of objects (MBM packets and feed packets are collections of ID_{50}s.

  Regarding the specific questions asked in this paragraph:

  - Q1: What are the mathematical equations in the simulation model? A. See answer above. Of course, we do specify equations in some cases where doing so makes sense – e.g., the change in susceptibility with age (see Section 2.3.4 in Appendix 1).

  - Q2: What are the exposure assessment models? A: We developed the exposure model (*i.e.*, we "assessed" exposure) based on information describing feeding practices. The discussion in Section 3.1.1.3 and the corresponding parameter specifications in Appendix 1 represent our exposure model.

  - Q3: Do they correctly represent the simulation process? A. Yes.

- Q4: What are the dose response equations? A. We refer the reviewer to Section 3.1.1.4 and the associated text in Appendix 1.

- Q5: How are the risks calculated based upon exposure assessment and dose-response relationships? A. The report's description of cattle exposure to contaminated feed, together with the description of the BSE dose-response relationship amount to a description of the risk that cattle will become infected with BSE. The report also describes human exposure to BSE, but does not quantify the risk of developing the corresponding human disease (vCJD) because there is inadequate information to quantify the dose response relationship (see, e.g., Section 1 in the report).

- Comment (1) – Paragraph (3) – The report already provides the information requested in this paragraph.

- Comment (2) – The October, 2003 report completely revises the sensitivity analysis. The report now considers each parameter and either provides a quantitative analysis of its impact on the results or a qualitative explanation as to why such an analysis is not necessary (see, *e.g.*, Table 3-10). Regarding "Spanish hypercube" – we are unaware of this methodology, but are aware of "Latin hypercube," the purpose of which is to more efficiently sample the tails of the probability distributions in a Monte Carlo simulation. We did not use Latin hypercube techniques because of the complexity involved in their implementation. However, as noted in response to comment (4) in this section, we believe that our simulation achieved sufficient resolution nonetheless.

- Comment (3) – We are not sure what the reviewers are referring to in this comment. Specific examples and suggested alternatives would be helpful.

- Comment (4) – While the November, 2001 report results were based on 1,000 simulation runs per assumption set or scenario, the October, 2003 report has increased the number of runs to 5,000 per assumption set or scenario. In addition, we report the 95% confidence interval for selected statistics for all scenarios run (see report Appendix 4). The results indicate that numerical stability is sufficient for the purpose of understanding the basic behavior of the agricultural system.

8 Appropriate Characterization of the Risks

- Comment (1) – The information requested by the reviewers is provided in the report. See response to Section 7, Comment (1).

- Comment (2) – First, we evaluated the model by comparing the predicted number of clinical cases (*i.e.*, animals showing visible signs of disease that are apparent without having to resort to a tissue sample test) to the observed number of such cases. We used the number of clinical cases as our comparison quantity because there were no data on the number of test-detectable animals from that period.

That being said, it is still true that the simulation results in our report understate the predicted number of clinical cases. The underestimate amounts to approximately a factor of two when the 50th percentile simulation result is compared with the number of reported cases.

Although the November, 2001 simulation results do not match the empirical results, it must be kept in mind that the simulation estimates were made without altering any of the parameters in an effort to better fit the empirical data. The November, 2001 report findings reflect our "best guess" at a reasonable set of parameters for this scenario. The October, 2003 report retains the "best guess" scenario described in the November, 2001 report, with some minor changes to implementation dates based on comments from the Swiss Federal Veterinary Office. In particular, we corrected the implementation date for the Swiss ruminant feed ban, making it December, 1990, rather than January, 1990.

In addition, the October, 2003 report describes two variations on the "best guess" Swiss scenario. The modifications made to the "best guess" Swiss scenario are in both cases modest and are consistent with the information available about conditions in Switzerland at the time of BSE was introduced into that country (see report Section 3.4.1). The first alternative scenario (Swiss Alternative 1) is the same as the "best guess" scenario except that the contaminated feed is divided among more cattle. As a result, less infectivity is "wasted" on the exposure of cattle that have already received enough exposure to guarantee their infection. Swiss Alternative 2 considers the possibility that additional contaminated feed was introduced into Switzerland. The results indicate that these modest modifications are sufficient to yield simulation results close to the empirical observations (see report Figure 4-9).

- Comment (3) – The emboli issue was addressed in detail for two reasons. First, without a quantitative analysis of this issue, it is difficult to dismiss it out of hand. Second, although emboli are less of an issue at present (because the use of pneumatic stunners in the U.S. has been phased out over the last several years), we designed the simulation to also model past conditions. For example, when cattle were imported during the 1980s from the UK into the U.S., pneumatic stunners were still in use, and as a result, the emboli issue was more of a potential problem.

- Comment (4) – Because a field analysis of compliance with the FDA's feed ban was beyond the scope of this study, we instead used a mass balance approach to determine the potential magnitude of this problem (our general approach is described in Section 2.16.4 in Appendix 1 of the H-T report). As the results of our analysis suggest, we did <u>not</u> assume that violations of the feed ban were necessarily limited in scope. In particular, our base case assumption is that 5% of feed and 5% of MBM is not only mislabeled, but is treated as if it is non-prohibited material. The worst-case assumption for mislabeling of prohibited MBM is 10%, while the worst-case assumption for mislabeling of prohibited feed is 33%.

- Comment (5) – The October, 2003 report now states (line 2022), "*Dairy cows are culled as they age primarily when their reproductive and production capacity become inadequate.*"

- Comment (6) – Regarding the dose-response – we used only the linear dose-response relationship. The sigmoid dose-response was described only for the purpose of qualitative comparison. Regarding maternal transmission – we included the potential for maternal transmission because we wanted to be sure that all plausible means of circulating infection within the agricultural system were accounted for (see our general discussion of the purpose of this analysis in Section I, above). We do not understand what is meant by the final sentence in this comment.

9 Identification and Characterization of Variability, Uncertainty, Critical Assumptions and Data Gaps

9.1 Key Sources of Variability and Uncertainty

- Comment (1) – The comment does not call for a response or modification. However, we note that the sensitivity analysis now evaluates only the base case and worst case assumptions for reasons described in the introduction to Section 3.2 (line 2533) ("*Typically, sensitivity analysis also involves estimation of risk for each parameter's best case value…*").

- Comment (2) – The October, 2003 report now correctly refers to the methodology as a "sensitivity analysis." The October, 2003 report also evaluates the impact of assigning worst-case assumptions to multiple assumptions simultaneously.

- Comment (3) – Characterizing variability in risk among cattle was beyond the scope of this report. USDA did not pose any policy question that would require quantifying the extent to which different groups of cattle might be at risk of developing BSE, although qualitatively it is clear which groups are candidates based on their consumption of MBM. We note that the simulation output could be modified to quantify risk for subgroups of the cattle population.

  Human food consumption data sufficiently detailed to quantify risk among different demographic groups were not available.

- Comment (4) – The comment does not call for an response or action.

- Comment (5) – Although the October, 2003 report tests two values (the worst case and base case value), these two values differed substantially (50% and 90%, respectively). Testing intermediate values would have produced results that generally fall between the predictions generated by the use of the base case and worst case values (stochastic "noise" introduced by the finite precision of the simulation might produce some results outside these bounds but the deviation would be small).

- Comment (6) The inconsistency noted by the reviewer has been corrected. Regarding the parenthetical comment, we do not know which decimal place the reviewer believes is not in the correct place.

- Comment (7) – The October, 2003 report now considers the potential impact of simultaneously assigning worst-case values to multiple parameters. Regarding the bounds used – we agree that wider bounds on the uncertain assumptions would yield a wider range of results. The reviewers have not identified any specific alternative values for the bounds assumed for any specific parameters.

- Comment (8) – The reviewer has listed several means by which additional infectivity might contaminate non-prohibited material. We assume a non-zero contamination rate for both renderers and feed producers. The reviewer does not specify how these assumptions should be changed or why these assumptions do not already reflect the contamination pathways he has identified.

- Comment (9) – The reviewer does not specify what specific alternative assumption we should test. Nor has the reviewer explained why changing the assumed incubation period would be expected to substantially influence the simulation's results.

- Comment (10) – As explained in the introduction to Section 3.2, we did not conduct a probabilistic uncertainty analysis because information to develop meaningful distributions for alternative parameter values is not available.

    - Q1 – How was the value of an input altered? A: Two values were tested (base case and worst case).

    - Q2 – The Monte Carlo simulation uses conventional sampling (as opposed to Latin Hypercube sampling, for example). The exact sampling algorithm is described and documented in the simulation computer code.

9.2 Critical Assumptions

- Comment (1) – The reviewer offers no alternative assumption or source of information to develop such an alternative assumption. Moreover, the sensitivity analysis indicates that changing the value of this parameter does not substantially influence the model's results.

- Comment (2) – The values we developed were based on FDA data. The reviewer does not offer either alternative values or specific information that could be used to develop such values. Finally, the sensitivity analysis indicates that changing the value of this parameter does not substantially influence the model's results.

- Comment (3) – The October, 2003 report includes a revised sensitivity analysis. Section 3.2, which describes the alternative assumptions, follows the structure of Section 3.1, which introduces each of the base case assumptions. Table 3-10 summarizes our treatment of each assumption (for some assumptions, we quantitatively evaluated the worst case using the simulation model, while for others, we qualitatively dismissed the need to quantitatively evaluate the worst case values). Regarding the values we selected for bounding values, we state that in many cases, our selections reflect our best judgment given the (limited) available evidence.

- Comment (4) – The change described by the reviewer reflects not a change in the actual prevalence but a change in the number of detected cases because of changes in surveillance practices. The model predicts the actual number of infected animals and the actual number of detectable animals (*i.e.*, animals with visible signs of disease). Neither of these values depends on the types of changes described in this comment.

9.3 Important Data Gaps

- Comment (1) – We have addressed this type of comment elsewhere (see *e.g.*, Comment (3) in Section 8).

- Comment (2) – Quantifying the probability of importing material from third countries is beyond the scope of this analysis (see our general comment on purpose of analysis in Section I, above).

- Comment (3) – The import of MBM could have been a potential pathway of entry into the U.S. for BSE and the October, 2003 report specifically addresses one version of such a scenario (*i.e.*, the contemporary import of contaminated feed). We note, however, the EC SSC GBR conclusion that the risk posed by MBM imports to the US is negligible. At the same time we note that the scenarios developed to evaluate the impact of cattle imported before 1989 (our UK imports scenarios) characterized the prevailing conditions of the 1980s and hence provide some indication of what would have happened had contaminated MBM been imported at that time. In particular, such MBM would have presumably infected some number of cattle that would have then entered the agricultural system and infect other cattle in the same way that infected cattle entered the system in our UK imports scenarios. The results would therefore be similar, depending on the amount of contamination hypothesized.

- Comment (4) – Tallow may be worthy of greater scrutiny in the future. Our treatment was informed by the demonstrated lack of BSE infectivity in tallow up to this point.

10 Usefulness of the Results for Risk Management

- Comment (1) – This comment poses three questions:

    - Q1: How do we know that the results are correct? A: As noted earlier, all aspects of the simulation have been completely documented in the report. In addition, the simulation code was made available to the reviewers and will be available to the general public.

    - Q2: What is the variability across different individuals or different scenarios? A. We were unable to identify food consumption data sufficiently detailed to quantify how risk varies across different population segments. Such data would have to quantify consumption of

different cuts of beef. We do not understand the part of the question asking about variation across scenarios. The report clearly describes the results for each of the many scenarios evaluated.

- Q3: What is the uncertainty in model outputs that derives from uncertainty in all inputs. A. The October, 2003 report evaluates the impact of assigning worst case values to multiple parameters simultaneously.

- Comment (2) – This comment does not call for any response or action.

- Comment (3) – We do not understand this comment. The model can be used to predict what might happen if BSE were introduced into the U.S. and what practices could help reduce the extent of its spread. The fact that BSE has not been detected does not mean that it could not be introduced in the future or even that it has not already been introduced.

- Comment (4) – Regarding the suggested evaluation of risk management measures to prevent the import of feed potentially infected with BSE – this is beyond the scope of the H-T report (see our general comment on purpose of the analysis in Section I, above). Further evaluation of FDA feed ban adherence (*e.g.*, through field studies) or development of methodologies to assess the value of this parameter are likewise beyond the scope of this analysis.

- Comment (5) – It is not clear to us what the reviewer envisions. The model allows specification of probabilities for a variety of events (*e.g.*, misfeeding, missplitting, and so forth). A model that computed these probabilities from the specification of a regulation does not seem plausible to us, or at the very least, it would be far more complicated than the model we have already developed. We developed the model in part so that users could identify those probabilities that most influence the spread of BSE and potential human exposure. We assume that once the users have identified these probabilities, they will develop the necessary regulations to effect changes.

- Comment (6) – See comment (4) in Section 9.2. Paragraph 2 – Presumably, any new tests would decrease the spread of disease to levels below those that we predicted.

- Comment (7) – This comment does not call for any response or action.

11 User Friendliness of the Model

- Comment (1) – This comment does not call for any response or action.

- Comment (2) – The model has already been made available to USDA, along with documentation. Although development of a user-friendly model is not part of this project, we will be making the model available to the general public after the review of our analysis is complete.

- Comment (3) – We do not know what particular assumptions the reviewer is referring to. We have used distributions we believed to be appropriate for each set of assumptions.

- Comment (4) –

    - Bullet (1) – We acknowledge this point in our discussion of the model's "validation" (Comment (2), Section 8).

    - Bullet (2) – Our model found that when we introduced even substantial quantities of BSE into the U.S., the prevalence of the disease generally decreased over time and was eventually eliminated. We believe this statement holds true even for those introduction pathways we did not test. The fact that we don't know how likely those introductions might be does not mean that we cannot predict what might happen if such an introduction occurred.

    - Bullet (3) – We acknowledge the potential impact of even a single case in the U.S. on consumer confidence. However, this point is outside the scope of our analysis.

    - Bullet (4) – The qualifying word in that sentence is "appears" (line 341). If the assumptions and the model are valid, then there is no potential for a BSE epidemic. We use the word "appears" to indicate that the reality of the matter may differ from our results.

    - Bullet (5) – The time period associated with that statement is indefinite. That is, there will be only three additional cases in total, no matter how long one waits. The details of the simulation are extensively documented in the body of the report.

- Comment (5) – While the reviewer suggestions would be desirable, they are beyond the scope of the project performed for USDA, which had no provision for development of a user-friendly model that can easily be used by a wide range of users. However, the documentation in Appendix 1 of the report does provide the necessary information to install and use the model for the interested investigator.

- Comment (6) – Development of a user friendly windows-based GUI program is well outside the scope of this project. Part of this limitation reflects the fact that the modeling of BSE is very complicated. There is therefore no way to make a program that is easy to use. However, although this model will never be easy to use, it will come with enough documentation for interested investigators to use it.

- Comment (7) – USDA personnel have been trained to use the model and documentation is available in Appendix 1 for others.

- Comment (8) – We acknowledge that the file format requirements are stringent. Although a more forgiving set of requirements could be programmed, doing so was outside the scope of this project.

- Regarding the reviewer question about the listing of the parameter files – as explained in Appendix 1, the user can divide the parameter definitions among any number of files he or she chooses (so long as a single definition is not divided between two files). All those file names must be listed in the file that is provided as an argument to the madcow simulation program.

- We disagree with the reviewer's suggestion that it would be better to have the program prompt the users on the command line for various parameters. Given the number of parameters and their complexity, this approach would be hopelessly complicated and error-prone. It would also make it difficult, if not impossible, to arrange batch-style execution of the simulation. Finally, it would complicate re-use of the same parameter files for multiple simulations, a feature that is very useful when testing scenarios that are very similar to one another.

- We do not doubt that a GUI (graphical user interface) could be developed for this software. However, doing so was beyond the scope of this project. We disagree that a GUI could have been developed in the time it took us to develop the code to read in the ASCII files.

- Comment (9) – See our response discussing the discrete event nature of this simulation (Comment (1), paragraph (2), Section 7).

- Comment (10) – While the reviewer may not have adequate time or resources to review the simulation software, we maintain that the documentation in the report and the code itself is adequate for its review by third parties.

12 Editorial Comments

For the most part, we have made the suggested revisions specified in this section. Our comments are as follows:

- Comment (14) – The text references the following source to support the pattern of age dependency illustrated in Figure 3-8: Collinge, J. and Palmer, M. (1997). Human Prion Diseases. *Prion Diseases*. J. Collinge and M. Palmer, Oxford University Press**:** 18-49.

- Comment (15) – Footnote (b) to Table 3-11 (line 2908) has been reworded as, "*We assume that the spontaneous CJD case observed in a young child was spongiform degeneration of infancy erroneously coded as CJD.*"

- Comment (16) – Text has been added to address this comment (line 2924): "*The number of animals was chosen arbitrarily to bound any potential introduction.*"

- Comment (17) – The value of 600 ID_{50}s is explained by the following text (line 2965): "*… we estimate the average number of ID_{50}s in a sheep to equal the time-averaged ID_{50} burden in cattle over the period prior to the development of clinical signs. This average is approximately 600 ID_{50}s.*"