Appendix 4 – Revisions and Responses to Peer Review Comments

Introduction

This appendix details Harvard's responses to peer review comments and notes changes to the model made in response to those comments. The Harvard responses appear in red.

In addition to the revisions made, as detailed below, Harvard has fixed an error discovered in the code since the release of the last version of this report. The error caused the model to incorrectly calculate the proportion of the incubation period that had elapsed at the point of slaughter or death. This error had virtually no impact on the estimated spread of the disease among cattle. For example, in the base case with 500 infected animals introduced, the number of new BSE cases over a 20 year period remained the same (180). The estimated value of R_0 also remained unchanged (0.24). Upper percentile estimates for these output values also appear to have remained virtually unchanged. On the other hand, the error caused the model to overstate potential human exposure to the BSE agent. For example, total mean exposure over the 20-year simulation period for the base case (500 infected animals introduced) decreased from 4,800 cattle oral ID_{50}s to 3,800 cattle oral ID_{50}s.

Response to Reviewer #1

Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update, Phase 1A

Comment on document dated June 1, 2005.

Remit

I have been asked to comment on this document in accordance with instructions to referees issued with the document, and taking into account the brief to Harvard from USDA. It will be obvious that one or two criticisms of the risk assessment should really be addressed at the remit, especially issues arising out of misinterpretation of the recommendations of the International Review Sub-committee.

As I am not myself a modeller I have focussed primarily on the manuscript, together with some of the underlying assumptions where accessible. I have also taken into account the first Harvard report of 2001, the revision that followed the 2003 Canadian case, and some raw data made available to the International Review sub-committee or held on the USDA or FDA web-sites.

General Comments

Corrections and additional information

a) **Section 2.2.3 – paragraph 3** – the statement "assuming an incubation period of 36 months, which has been typical in the pathogenesis study" – must be verified and corrected where appropriate. Firstly, the two pathogenesis studies conducted at the VLA have involved sequential slaughter of cattle. Only details of the first study have been published. It is not possible to derive a typical incubation period from such a study. Clinical onset was first detected at 35 months in one animal, but this cannot be taken as representative of a larger population. Some of the cattle slaughtered at earlier time points may have died of BSE sooner if they had not been proactively killed. Additionally the challenge dose was high, at 100g, and would inevitably have led to a shorter incubation than for most natural exposures. The first sentence of this paragraph is indeed superfluous as the relative proportions of infectivity in the body can be taken directly from SSC/EFSA opinions, taking into account the DNV calculations. There is no need to take into account the 36 month incubation unless attempting to establish infectivity levels at a particular time point (see para b).

   It is unlikely that a revision to this parameter would have a substantive impact on the results. In the base case analysis, tonsils contributed an average of 0.03 ID_{50}s to potential human exposure over a 20-year period, out of a total potential human exposure averaging 95 cattle oral ID_{50}s.

We request that the reviewer provide the estimates referred to for the proportion of infectivity in tonsils. Perhaps this information available in the article cited by the reviewer in review comment (c). Provision of such an estimate would allow us to eliminate the computation making use of the 36-month incubation period.

b) **Section 3.3, Sensitivity 6** – the same error is perpetuated in a personal communication from myself. The study referred to which gives dose response data is the "Attack Rate study." This should be corrected to avoid later confusion.

"Pathogenesis study" has been changed to "Attack Rate Study" in the first paragraph of Section 3.3, Sensitivity 6.

c) **Section 2.2.3** – reference to the EFSA report should also include the primary data published in Wells GAH, Spiropoulos, J, Hawkins SAC and Ryder, SJ. (2005). Veterinary Record. 156. 401-407. Pathogenesis of experimental bovine spongiform encephalopathy: preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle. I can supply a pdf copy if required.

Done.

d) **Section 3.3 Sensitivity 6** - The authors should be aware of a new assessment of age susceptibility by Arnold ME and Wilesmith JW. (2004). Preventive Veterinary Medicine. **66**. 35-47. Estimation of the age-dependent risk of infection to BSE of dairy cattle in Great Britain.

That you for the suggestion, although it is not clear at this time how citing the article identified by the reviewer, which talks primarily about susceptibility as a function of age, would directly support the material in Section 3.3. That section addresses the issue of incubation period as a function of the magnitude of the infective dose.

e) **Secion 3**.3 Sensitivity 6 – If not already aware, the authors may wish to note the following paper in considering the likelihood of infected animals surviving to clinical onset. Donnelly, CA, Ferguson, NM, Ghani AC and Anderson RM. (2002). Proceedings of the Royal Society of London. Series B. **269**, 2179-2190. Implications of bovine spongiform encephalopathy (BSE) infection screening data for the scale of the British BSE epidemic and current European infection levels.

We appreciate the suggestion but do not understand from the reviewer's comments what statement in the text should be added, or how the identified article supports statements already in the text.

Specific Comments

a) **Executive summary, p5, para 4**- it is surprising in this context that cross-contamination is considered to be a relatively minor factor in potential transmission. This conflicts with European experience, but I will discuss further below.

See our response below to comment (h).

b) **Executive summary, p5, para 5** – again to be discussed below, I think the effectiveness of the recommendation by the International Review group is underestimated, primarily because of misinterpretation of its intent. The recommendation would have included SRM from dead stock, as applies in Europe. Indeed it is the primary reason for requiring destruction of deadstock in Europe as these and their SRM were recycled in the past.

This issue has been fixed – see response to USDA Comment 2.3.3.

c) **2.1.2** – some consideration should have been given to the likelihood of failing to correctly identify the age of cattle at slaughter. There is anecdotal evidence that this occurs, and experience in the UK would suggest that this is a risk area, especially in the absence of more rigorous forms of identification and certification of age.

We are not claiming that the probability of passing antemortem inspection depends on the inspector knowing the animal's age. Instead, we take into account the likelihood that an older animal is less likely to pass inspection than a younger animal simply because the older animal is more likely to have physical problems than the younger animal. As described in Appendix 1, we assume that age has at most a modest influence on the probability of passing antemortem inspection.

d) **2.1.2** – also to be discussed later, but I believe that there is a tendency to overestimate the ability to detect clinical signs at the abattoir. This has been highlighted by the detection of cases through active surveillance in Europe, which, with hindsight, were demonstrating clinical signs compatible with BSE, and were clearly not prevented from being slaughtered as healthy cattle.

See response to paragraph (e).

e) **2.2.2** – I'm not entirely sure what "inspector flunks 90% of all animals with clinical signs means". If it means that he/she misses most of them then this could be true. For clarification of points in para d) above.

   a. For ambulatory cattle, some recategorisation of UK surveillance data may help to understand the problem. They are relevant in the sense that the UK can now be considered a country where BSE is no longer expected to be seen regularly, as in most other countries, and where competence in identifying such cases may be declining. In the UK Over Thirty Months Scheme in 2004, a total of 291,080 animals passed ante-mortem

inspection, but 8 proved to be positive for BSE. None were identified as suspects at ante-mortem inspection. In contrast 14202 animals did fail ante-mortem inspection, of which 11 were positive. In 2005, the equivalent figures are (to 5 August) 149,653 passed ante-mortem inspection and 6 proved positive. 9076 failed ante-mortem inspection, and 5 were positive. Again, in neither category were the positives identified as BSE suspects at ante-mortem inspection. Retrospective investigation of such cases indicates that the majority present with signs consistent with BSE, but were not downers. So it seems as if only approximately 50% of clinical cases may be detected at ante-mortem inspection at abattoirs in the UK at present, and even then they are still only identified as "risk animals" rather than as BSE suspects. I believe that EU data suggest even lower detection rate. At one time the German epidemic consisted solely of animals detected in the slaughter chain where clinical evidence had been missed.

b. For non-ambulatory animals it is more difficult as our current statistics do not break down cases that failed ante-mortem inspection into ambulatory or non-ambulatory. I have therefore presented data below (appendix 1) that represents the field scenario, namely where State Veterinarians were presented with suspect BSE cases that were not sufficiently convincing to warrant compulsory slaughter, but where slaughter was carried out voluntarily. In many instances this group consisted of downer cows, and the difficulty of conducting an appropriate clinical examination meant that suspicion of BSE could not be distinguished from the many causes of fallen animals. The diagnostic rate for the epidemic so far for such animals is 63.31%, but has varied from year to year from 88.14% in 1988 to 11.32% in 2004. It is inevitably decreasing as the epidemic declines, and consequently a low diagnostic rate might be expected against a background of other neurological diseases that will continue. Given that this category in the UK will include some ambulatory animals, it may be appropriate to consider a diagnostic rate of 40-60% for this category rather than 85% adopted so far.

First, our statement that 90% of animals with clinical signs "flunk" inspection means that we assume inspectors detect 90% of the animals with clinical signs.

We agree with the reviewer that the data from the UK and EU suggest that it would have been more appropriate to assume that a smaller proportion of animals with clinical signs are detected by inspectors. Sensitivity Analysis 5 addresses this issue by assuming that 50% of ambulatory clinical cases and 25% of non-ambulatory clinical cases are detected. These assumptions would appear to address the reviewer's concern that overall detection of clinical cases would be approximately 50%, with detection of non-ambulatory clinical cases as low as 40%.

The impact of these assumptions on the model's predictions for animal health is minimal (*e.g.*, the mean number of new BSE infections increases from 180 to 190 animals over 20 years). Human exposure does increase by about 50%. If our pessimistic antemortem inspection assumptions are deemed more appropriate than the base case assumptions, the results from other scenarios can be adjusted by increasing projected human exposure by approximately 50%. In any case, it must be kept in mind that the absolute level of human exposure remains very small, amounting to 7,500 cattle oral ID_{50}s over a period of 20 years following the introduction of 500 infected animals into the U.S.

f) **2.2.2 – final paragraph** – it will be interesting to see the outcome of analyses if ability to detect and exclude clinical cases is revised in accordance with my comments above.

See response to comment (e).

g) **2.2.4** – it is a pity that with the passage of time the audit details of feed controls has not generated sufficient precision to enable meaningful assessments of compliance levels in the model. Indeed the changed format for reporting appears to have made modelling more difficult than in the past. While the authors are cautious in using data gathered before 2003, rather than later audit data which might be expected to represent improved compliance, I am still concerned that the original assumptions still do not represent the true situation. Furthermore, this may well have varied with time and geographically, and it is inevitably difficult to model that risk.

We are unaware of better data to quantify this set of assumptions. Moreover, Sensitivity Analysis 1 (pessimistic MBM/feed production mislabelling and contamination assumptions) addresses the possibility that the base case values for these parameters are incorrect.

h) **2.2.4, table 1** – the term "cross-contamination" in the European context is represented by the term "commingling" in table 1. From the evidence of compliance levels across the board in the early post-ban period, and experience in Europe, and taking into account susceptibility to low dose, I consider this element to continue to be underestimated. This does not necessarily imply continuation of a propagation phase, but in the absence of significant volumes of circulating infectivity it does potentially give rise to potential sporadic cases as detected by active surveillance. In the presence of significant circulating infectivity then it could lead to a prolonged European-like low level epidemic. I'm not disputing the outcome of the model, simply the assumption that the risk of commingling is low.

We interpret this comment as suggesting that we have understated the likely proportion of feed and MBM contaminated *via* commingling. Note that results from our October, 2003 risk assessment suggests that the incremental impact of

pessimistic assumptions for the commingling parameters is limited (see Sections 2.3.2 and 2.3.4 of Appendix 3A in that risk assessment). We agree that commingling slows the rate at which BSE is eliminated from a cattle population after it is introduced. However, in the U.S., our results suggest that commingling would not substantially extend the presence of the disease in this country. Finally, note that the prolonged low-level BSE situation in Europe is likely to arise from other factors in addition to commingling.

i) **2.2.4, table 2** – From our experience in the UK, I suspect that while the outcome of cross-contamination is similar to that presented in table 2, there will have been rare occasions, especially with contaminated feed rather than MBM, where a much greater proportion of prohibited material will have transferred during a contamination event. Such instances gave rise to positive results where finished feed was tested on farm. For the production of MBM this is perhaps less likely, other than in situations where prohibitions have introduced differential pricing of commodities. In other words, loss of value of a raw material because of a prohibition increases pressure on the producer to sell it fraudulently, disguised as a different raw material. eg. ruminant protein sold as fishmeal. I have insufficient knowledge of the impact of such measures on US trade in such commodities to recommend alternative assumptions, but if there is evidence for such pressures then some reconsideration may be necessary. There may have been real incentives to do so if the perception was that it wouldn't matter anyway as BSE wasn't present.

   We are unaware of evidence suggesting higher rates of mislabelling or commingling. Our report investigated the impact of more pessimistic assumptions (scenario Sensitivity 1) and found that the impact of these assumptions on the model's predictions is modest.

j) **2.2.5** – since 2003 there has been reconsideration of risks associated with DRG in the UK and Europe, and a recognition that those from the lumbar area are more likely to be consumed with deboned meet than are those from the cervical and thoracic areas, because they lie more remotely from the vertebral column. This determines how much infectivity remains with the vertebral column and how much with the meat, following deboning. This work was only a small study, and I don't believe has been fully published or resulted in significant changes to the UK modelling of risk from DRG. I will however attempt to obtain further clarification of this issue.

   Because of the limited data on this topic, there is no basis for revising assumptions at this time.

k) **2.2.6** – it is a pity that even after the Canadian cases the authors appear unable to take into account the geographical implications of importation of both cattle and feed. The importations remain hypothetical, and inevitably fail to trigger alarm

bells that might be associated with relatively focal introduction of risk. Indeed the initial reassessment that was conducted following the 2003 Canadian case appears not to be taken into account there, presumably because it is still considered to be within the scope of the worst case scenario. In addition, the authors should perhaps consider the implications of the BsurvE model developed by John Wilesmith and others, and adopted by the OIE to consider the implications on distribution of infected animals in different sampling chains at different time points following introduction of infectivity. Inevitably, it is only when one reaches the clinical phase of an epidemic where the high risk populations (BSE suspects, fallen animals, casualties) represent the majority of cases. The majority of infected animals will however have been slaughtered for human consumption while presumed healthy, and at least a proportion of them will have been CNS-positive.

It is true that there is evidence that BSE has been introduced into the U.S. and moreover, there is a risk that imports from Canada could result in the import of additional BSE-infected animals. However, the likely magnitude of such introductions remains well within the scenarios evaluated in our report (10 to 500 infected animals). Keep in mind that the purpose of this analysis has been to evaluate how different measures affect the spread of BSE in the U.S. following its introduction. It is not the purpose of this analysis to evaluate specific introduction scenarios.

l) More disturbingly at this stage is that the modelling conducted after the 2003 Canadian case recognised that the introduction of infectivity in feed was a greater danger than the introduction of infected cattle. All this remained hypothetical at the time. Nevertheless, in this model it appears as if feed-borne transmission appears only to be considered as a consequence of recycling of infectivity introduced in live animals. Imported Canadian cattle, and imported Canadian meat and bone meal, represented additional seeding points, possibly localised, where because of local circumstances the risks may have been greater than recognised by the base case or the national worst case currently presented in this document. I realise that imports of meat and bone meal were small, and are believed to consist of non-ruminant material, but imports of feed were significant. It may well be that the outcome is still considered to be accommodated within the upper limit used as worse case, but I do wonder if such modelling holds true if the input of infectivity was localised. The importations will also certainly have been later than were considered in the 2003 risk assessment. The Canadian cases have highlighted the parochial nature of initial propagation, as occurred in the UK, and consequently the outcome is highly dependent on **where** the infectivity entered the feed chain, whether from indigenous or imported cattle, or contaminated imported feed. They have also highlighted deficiencies in the historical feed controls in Canada.

The distinction between introduction of BSE into the U.S. *via* import of live cattle *vs.* introduction *via* import of contaminated MBM or feed is not important for the

purpose of this analysis. As stated in response to comment (k), the purpose of this analysis is to compare how alternative measures influence the spread of BSE following its introduction.

An earlier analysis conducted by Harvard (Cohen 2003) did compare the impact of importing from Canada (prior to implementation of the 1997 feed ban) live animals infected with BSE to the impact of importing contaminated feed from that country. The main difference was that feed lead to a faster increase in the number of BSE cases in the U.S. because the infectivity it harboured was immediately available to expose domestic cattle. On the other hand, imported cattle infected with BSE did not immediately infect other animals because of the delay between import and slaughter assumed. This difference in delay resulted in a larger number of new domestic BSE cases following the import of contaminated feed because additional time was available for BSE to spread prior to the implementation of the 1997 feed ban.

Finally, we note that while it is possible that feed may harbour a substantial amount of BSE infectivity, it is difficult to imagine that the resulting impact would be greater than the impact of importing 500 BSE-infected cattle.

m) **2.3.3 – modelling proposals of the International Review Committee** – this paragraph clearly states that the first option was intended to remove SRM from the **human and animal chain**. ***From the European perspective fallen animals also contain SRM, and the term is not restricted to animals slaughtered for human consumption.*** It is difficult 18 months later to recall the exact position of all sub-committee members on this precise subject, but we did recognise that SRM represented the primary source of infectivity for both human and animal food/feed chains, and in light of a feed ban that continued to allow ruminant protein to circulate and be incorporated in non-ruminant feed, the exclusion of SRM was critical. The exclusion of SRM from healthy animals, but not that from high risk animals, inevitably leaves significant quantities of infectivity in the feed chain.

Fixed – see response to USDA Comment 2.3.3.

n) **2.4 – sensitivity analyses**

a. sensitivity 4 – despite my suggestion that the authors should consider new data on removal of DRG, it is likely that the range of risk, still small, is encompassed by the scenarios considered.

   See response to comment (j).

b. Sensitivity 5 – further consideration may be needed in light of data provided above.

   See response to comment (e).

c. Sensitivity 6 – in this context it may be worth considering incubation periods in BSE cases born in the UK after the 1996 feed measures, where exposure is presumed to be to low doses, but where the incubation range, although raised slightly, has remained within that experienced earlier in the epidemic. This data should be available from John Wilesmith. The incubation range following experimental oral exposure also appears not to be unlimited, with the longest so far following exposures to doses as low as 1mg being 75 and 76 months at 1 and 0.1g respectively. The singleton cases in the 0.01 and 0.001g dose groups were within this range. The study has now run 13 months since the last clinical case, but it remains to be seen whether any more succumb.

The purpose of this analysis was to illustrate the potential impact of assuming that the incubation period for BSE depends on infective dose. The information on the relationship between infective dose and incubation period is extremely limited. In addition, as explained in the discussion of Sensitivity Analysis 6 in Section 3.3 of our report, there are other uncertain assumptions that must be better resolved in order to estimate exposure levels for individual animals with greater confidence. These issues are: 1) the number of animals among which batches of feed are divided; 2) the assumed level of exposure among infected animals introduced into the U.S. at the beginning of the simulation; and 3) whether the assumed exposure is quantified in terms of susceptibility-adjusted ID_{50}s or in terms of ID_{50}s not adjusted to account for age-dependent susceptibility. Without further information, it is difficult to refine this sensitivity analysis.

o) **3.1.1, para 2** –This section should be clarified in order to emphasise that the introduction of active surveillance almost inevitably brings with it a danger that occasional cases will be detected during the elimination or end phase of an epidemic. If this is not made clear at least in subsequent responses to the document, each case detected, if any, will be used to undermine the claim of elimination in the report.

We agree with this point but believe it is beyond the scope of the report. The purpose of the report is to predict actual BSE prevalence and human exposure to BSE. For this reason we do not discuss potential empirical measurements of prevalence (for example) and how those measurements might depend on the type of surveillance program instituted.

p) **3.2 – alternative scenarios**. It would be nice in light of what I said at para m) above if the outcomes in tables 2 and 3 could be rerun with SRM also removed from deadstock before rendering. Even removal of the head alone should reduce the risk considerably and prove to be easier to audit than a more extensive removal of spinal cord and other organs.

See response to USDA comment 2.3.3.

q) With that exception, the effect of the measures on exposures to cattle and humans contain no real surprises given the underlying assumptions.

a. The outcome of FDA scenario 2 contrasts with the European experience, and it does suggest that there needs to be serious reconsideration of underlying assumptions.

See response to comment (h)

b. I am presuming that the term "misfeeding" means that farmers feed cattle on product intended for pigs/poultry to cattle, which would suggest an association of BSE prevalence with the keeping on the same farm of other species. This was not the case in Great Britain even in a period where there was a clear association with local pig/poultry population densities. The association was linked to the source of feed production, and not to farm-associated risks. I cannot deny however that there have been occasional cases where mis-feeding has clearly been a factor, but in a population sense this has had less significant than manufacturing risks. There is some evidence that it may have become of greater significance after the 1996 feed ban, with purchase of proprietary feed apparently being protective, but detail of this issue will need to come from John Wilesmith. The authors acknowledge under sensitivity 2 that the predicted spread is particularly sensitive to assumptions about the rate at which prohibited feed is fed to cattle, and it is with that in mind that I am disappointed that feed audits have not assisted in firming up the input data. Consequently the report form appears to fail to gather sufficient data on the potential for low dose contamination, and from past experience in the UK this format of form generated a significant degree of complacency in the context of auditing compliance with SRM rules.

No response called for.

r) **3.3 - Sensitivity analyses** – other than issues already raised above which might give rise to recalculation the authors may wish to take into account the publication by Donnelly et al (2004) referred to earlier, which estimates that up to 3.4 million cattle may have been infected in the UK, of which fewer than 200,000 have been recognised as clinical cases. The majority will have been consumed when young, and some will have died without suspicion of BSE. Also, the paper by Arnold and Wilesmith cited earlier may help in consideration of age-susceptiblity. The worst case scenario adopted for sensitivity 5 may well be closer to reality than the base case, as discussed previously.

See responses to comments (d) and (e).

Conclusions

a) The model remains sound, insofar as it can deliver precision in the absence of so much underlying data. Nevertheless, there is a need for greater clarity in ensuring that differences between this model and its predecessors are obvious and robustly explained.

We believe Section 2.1 of our report addresses this point.

b) Some remodelling may need to be done based upon changes of assumptions recommended above, but the outcome is not expected to change substantially. For human exposures the only major change would be a possible outcome closer to the pessimistic sensitivity 5 analysis with regard to ante-mortem detection. For animal health the disposal of SRM or as a minimum the head from deadstock, and its exclusion from animal feed, would have a significant impact on future exposures.

See response to comments (p).

c) At the moment it is of course difficult to predict exactly where the USA may be in the course of its epidemic, whatever its size, and this is dependent in part on the degree of compliance with the 1997 feed ban. Inevitably the effectiveness of some control measures may be expected to vary with time, and the optimum time for tightening of controls may already have passed. The current outcomes do not predict the chronology of an epidemic, and consequently it is difficult to comment on whether the measures evaluated are currently applicable.

No response called for.

d) The chronological and spatial analyses conducted on the BSE epidemic in Great Britain highlight the importance of looking at local events and local risks in that a national picture is composed of multiple smaller local foci. Given the size of the USA and likely influence on movements from one part of the country to another, it is conceivable that scenarios similar to the Canadian situation may have arisen. If at all possible a spatial risk assessment should be done with regard to risk arising from historical Canadian imports of both cattle and meat and bone meal.

Such an analysis is beyond the scope of this report. In any case, heterogeneity might have a substantial impact on disease spread only if there are relatively isolated segments of the U.S. agricultural system that have characteristics making them substantially more susceptible to the amplification of BSE. Data describing differences in these characteristics would allow modelling at a more local scale.

Annex 1

BSE cases with no Form C

Year of restriction	Positive	Total submitted	Diagnostic Rate
1988	602	683	88.14%
1989	487	656	74.24%
1990	976	1461	66.80%
1991	1387	2100	66.05%
1992	2064	3232	63.86%
1993	2021	3296	61.32%
1994	1619	2740	59.09%
1995	1026	1617	63.45%
1996	591	965	61.24%
1997	332	520	63.85%
1998	250	444	56.31%
1999	191	320	59.69%
2000	93	180	51.67%
2001	35	90	38.89%
2002	29	83	34.94%
2003	19	72	26.39%
2004	6	53	11.32%
2005	4	20	20.00%

Cohen, J. T. and Gray, G. M. (2003). *Evaluation of the Potential Spread of BSE in Cattle and Possible Human Exposure Following Introduction of Infectivity into the United States from Canada.* Boston, MA, Harvard Center for Risk Analysis.

Response to Reviewer #2

HARVARD PEER REVIEW 2

PROJECT TITLE: Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update Phase IA; June 1, 2005.

AUTHORS: Joshua T. Cohen & George M. Gray, Harvard Center for Risk Analysis.

REVIEWER: Kept Confidential by Contractor/FSIS

REVIEW QUALIFICATIONS:
Instructions provided to the review panel indicated that the following should be considered:

a. Evaluate whether the modeling approach adequately meets the goals and the tasks outlined in the Statement of Work for the Harvard BSE Risk Assessment (see Attachment A).
b. Review the available data and underlying assumptions used in this Risk Assessment.
c. Review whether the revised model adequately characterizes the uncertainty distribution of the potential human exposure for the regulatory analyses.
d. Are the effects of BSE-related policies implemented by USDA and proposed by Food [and] Drug Administration (FDA) since December 23, 2003 adequately modeled and evaluated?
e. Are the recommendations of the International Review Subcommittee adequately modeled and evaluated?
f. Review if adequate documentation has been provided for files (used and generated) and within source codes.
g. Adequate sensitivity analysis has been provided for the new baseline case.

It was assumed that the peer-review panel for this report includes individuals with differing disciplines of expertise and, to that extent, that differing reviewers will tend to focus on areas of the report that reflect those differences in expertise. This reviewer did not attempt to ascertain whether or not model source code and documentation included in files were appropriate, or whether or not specific modeling protocols overall were appropriate, as this reviewer is not perceived to have credible expertise in these areas. Furthermore, it was assumed that previous versions of the Harvard Risk Assessment also were subjected to peer-review and that, other than those modifications to the base case model discussed in the Harvard Risk Assessment report reviewed here, assumptions and other scientific evidence used in those previous Risk Assessment models were as accurate and realistic as possible. Therefore, this reviewer attempted to focus on the reasonableness and accuracy of assumptions and/or values associated with beef production and food safety practices that are described as being revised from the initial base case model in this report, as well as analyses and conclusions. Comments provided below addressed items b, c, d, e, and g listed in the "Instructions for Peer Reviewers." Comments are firstly formatted to reflect generalized editorial associated with content and major issues, followed by a detailed list of suggested technical revisions by page number.

GENERAL COMMENTS:

It was apparent upon review that a tremendous amount of human time and computing resources have been expended to complete this version of the Harvard BSE Risk Assessment; the Harvard Center for Risk Assessment and the USDA and FDA Agencies contributing to the overall effort should be commended. The approach generally seems logical and meaningful to USDA Agencies and FDACVM who are responsible for developing regulatory policy, and it was important that the BSE Risk Assessment considered risk to public health in addition to risk to animal health.

No response called for.

Increasing the number of infected animals introduced into the simulation for purposes of reducing the number of iterations of the model that were necessary to achieve precision equal to (or exceeding) that of previous Harvard Risk Assessment simulations (for purposes of reducing the number of simulation trials necessary to test the impact on risk of regulations imposed after December 23, 2003) was appropriate. Because precision is best measured as the variance associated with the mean response (i.e., the dependent variables of numbers of animals infected, public health risk via numbers of cattle oral ID50S, and the epidemic's basic reproduction rate = Ro), and precision may be controlled via (a) reduction in residual error about the mean or (b) increased numbers of observations, increasing the initial number of infected animals to reduce residual error was a reasonable option to achieve the desired precision while simultaneously minimizing resource requirements. The investigators clearly stated multiple times that the number of infected animals initially introduced into the model was generally academic—they recognized that "the introduction of 500 infected cattle into the U.S. is very unlikely." Subsequent assessments of risk reduction due to simulated shifts in regulatory policy generally yielded proportional responses (except, as stated, for percentile estimates). Generally, and in the context of the objectives of this endeavor, this did not appear to have deleterious effects on results or conclusions.

No response called for.

However, this reviewer did identify some technical concerns associated with both assumptions/values developed for use in the base case model and the manner in which results were presented relative to the "Goals" of USDA as outlined in the "Excerpts from Original USDA Statement of Work" (Attachment A to the "Instructions for Peer Reviewers"). These concerns may have serious interpretation consequences and are described and discussed below:

1. Section 2.2.1 concerning the modeling of "Assignment of Ambulatory Status" is confusing and may have resulted in the use of an inaccurate assumption within the base case model. Specifically, the authors stated that P(S,, A) and P(S,, NA) were derived from European Commission data defined (via footnote) as "fallen stock" which are "animals that have died or have been killed on the farm or in transport . . ." Ambulatory status only depends on the animal's clinical status to the extent that the animal is not dead. The cited

European data naturally would serve to best estimate the probability of an animal in an epidemic contracting clinical BSE, but it did not appear to allow an appropriate estimate of the probabilities that animals showing clinical signs of the disease would be ambulatory vs. non-ambulatory. Non-ambulatory animals are "downers" as described in lay terms in the U.S., but they are not "dead" animals—conversely, they are recumbent but alive. Thus, if indeed the European data cited were used to compute these probabilities, the values actually estimate the probabilities (in the epidemic situation) that cattle showing clinical signs of the disease may be "dead" vs. "not dead," but not the probabilities associated with the ambulatory vs. non-ambulatory condition. The authors made conclusions from model output as if the probabilities reflected impact of the "Downer" Interim Final Rule of January 12, 2004 when, in fact, they reflected probabilities of clinical cases of BSE being "dead" or "not dead." In addition to this, the probability of an animal being ambulatory vs. nonambulatory, P(A) vs. P(NA), is highly dependent on the parent population from which this probability estimate is computed; these values would differ substantially (as discussed below) for the fed beef vs. market cow/bull populations in the U.S.

See response to comment (2).

2. The potential ramifications of an error as described in Concern 1 above may be compounded, as may the influence on results of several additional assumptions made in the base case model, by not considering the fed beef (young cattle) population differentially from the market cow/bull (older, very mature cattle) population of slaughter cattle. Generally, the majority of cattle slaughtered in the U.S. (>28 million of the total 35 million slaughtered per year) are weaned from their mothers when they are less than 8 months of age. They are then pastured or grown in a dry-lot for an additional 4 to 11 months, and then fed a high-concentrate (high-energy) diet in a finishing feedlot for 100 to 150 days. Rarely are mainstream fed cattle slaughtered when chronologically older than 12 to 21 months of age; available data suggest that the mean chronological age of fed cattle at harvest is about 16 to 17 months of age. Currently, there are about 706 packing plants slaughtering about 17.2 million fed steers and 11.1 million fed heifers each year. The largest four packing firms slaughter about 81%, and approximately 29 plants operated by the largest five firms account for approximately 88% to 90% of the total number of U.S. cattle harvested each year. The typical large packing plant slaughters in excess of 5,000 fed cattle each day. Conversely, about 6.7 million mature, culled beef and dairy cows, bulls, and stags (which mostly comprise the "at-risk for having contracted BSE" population and are well over 30 months of age) are slaughtered in many more smaller and generally different plants each year than those in which fed cattle are slaughtered; these market cows/bulls reflect only a small fraction (about 19%) of the total 35 million U.S. cattle harvested each year and an even smaller number that are of a chronological age to have contracted the BSE infectious agent and show clinical signs of the disease. Thus, as one example of the need for differentiation in the risk assessment modeling process of these two cattle
populations, the probability of a U.S. fed steer or heifer being non-ambulatory [P(NA)] vs. ambulatory [P(A)] is rather remote (maybe 1 or 2 head per day in plants slaughtering 5,000 head per day—mostly due to broken appendages), while the same probability for market cows/bulls would be much greater (i.e., mature cows/bulls pre-January 12, 2004 were typically culled from the herd and slaughtered because they no longer were reproductively viable—they were culled not due to market incentives but, rather, because they were physically or clinically ailing). Likewise, the probability of a fed steer or heifer at slaughter showing clinical signs of

BSE and being non-ambulatory vs. ambulatory— P(S,, NA) vs. P(S,, A), respectively—is very remote (never detected), while the same probabilities for a culled market cow/bull at slaughter (generally >5 years of age) would be expected to be greater (e.g., the "Texas Cow" of November 2004 = 1 of about 6 million head per year in a single year). The study investigators should consider the effects of these substantially differing probabilities on the output results of the base case model; it is likely that other estimated probabilities utilized in model assumptions would differ as dramatically between these two populations (e.g., Section 2.2.2).

With regard to comment (1), we agree with the reviewer and have eliminated the derivation of probabilities for clinical signs given ambulatory status. In the absence of an alternative source of information, we have instead retained the original base case values and have evaluated the impact of alternative possible values on the simulation results.

For this purpose, we have conducted two sensitivity analyses. The first evaluates the impact of using a smaller value for the probability that animals without clinical signs will be non-ambulatory. The original base case value for this probability was 0.005. The sensitivity analysis considers a value of zero (note that reviewer comment #2 suggests this value is on the order of 1 to 2 per 5,000 for a fed steer or heifer). Assuming a larger value for this probability would decrease the proportion of animals ante mortem passing inspection, something that would decrease the spread of disease (and human exposure) even further than suggested in the base case.

The second sensitivity analysis evaluates the impact of using a larger value for the probability that animals with clinical signs will be non-ambulatory. The original base case value for this probability was approximately 8%. The sensitivity analysis investigates using a value of 1.0. Assuming a greater proportion of clinical animals are non-ambulatory modestly decreases the probability that they will be identified as at ante mortem inspection as having BSE because the probability of detection is 95% for ambulatory animals and 85% for non-ambulatory animals.

As the results show (see Sensitivity Analysis 7 and Sensitivity Analysis 8), these changes have at most a minimal impact on the results. We conclude that this source of uncertainty, while substantial, is not important for the purpose of our analysis.

3. Although, as previously mentioned, the investigators are to be commended for including an analysis of the risk of BSE to public health in the U.S. (i.e., by reporting results in terms of "cattle oral ID50S") and the impact of new USDA and potential FDA policies on risk to humans, concern should be expressed with respect to how these results may be interpreted by a lay audience. Specifically, and although the "cattle oral ID50S" is a measure of potential consumer exposure to BSE, it does not actually reflect risk in absolute terms to humans. A better approach would be to report these values in "human oral ID50S" (using the literature to make the computation if possible) such that results may not be misrepresented—particularly by un-informed foreign media.

As explained in our 2003 risk assessment, we have specifically not provided an estimate of human risk corresponding to the estimated potential human exposures to the BSE agent (quantified in cattle oral ID_{50}s) because the potency of the agent in humans, compared to cattle (the "species barrier") is very uncertain, with plausible values spanning four orders of magnitude (see p. 4 in Comer and Huntley (2003, *Exposure of the human population to BSE infectivity over the course of the BSE epidemic in Great Britain and the*

impact of changes to the Over Thirty Month Rule. 2003. DMV Consulting. OTMR Review Paper Ver 3, http://www.food.gov.uk/multimedia/pdfs/otmcomer.pdf). We agree with reviewer that without proper framing of the human exposure estimates, the public may not appreciate the limited nature of this exposure. While risk communication is beyond the scope of the report under review, we note that the exposure could be put into perspective by comparing it to plausible exposures experienced in the UK. We took this approach in our 2003 risk assessment (see p. viii of the Executive Summary).

4a. Sections 2.1.1, 2.2.2, 2.3.1, and 2.4 of Methods become confusing when one considers the conclusions of alternative scenario and sensitivity analyses. Generally speaking, and because no history (and, therefore, no data) exists to establish whether or not USDA-FSIS inspectors are capable of detecting BSE in ambulatory vs. non-ambulatory cattle during antemortem inspection, this reviewer accepts the probabilities of detecting clinical BSE during ante mortem inspection as specified (95% vs. 85%, respectively) for the pre-December 23, 2003 base case model.

No response called for.

4b. However, since implementation on January 12, 2004 of the new "Downer" regulation, non-ambulatory cattle are not allowed to be offloaded from trucks at packing plants—generally, non-ambulatory cattle are not presented for antemortem inspection. In addition, if an animal becomes nonambulatory following antemortem inspection, and neurological disorders are a concern (in other words, the animal shows clinical symptoms other than a broken appendage), then the animals are condemned before slaughter and are not allowed to enter the packing facility; in most cases, such cattle are killed in the plant holding pens and tested for BSE under the new surveillance program because they fall into the "high risk" category for having contracted BSE. Within the constraints of the "test-and-hold" policy, the carcasses of tested nonambulatory animals killed in plant holding pens post-antemortem inspection are land-filled, incinerated, rendered as inedible product, or digested for disposal if found to be negative for BSE via testing—it is presumed that an animal testing positive for BSE would be disposed of in a manner preventing further dissemination of the disease. Hence, the assumed (by the investigators) probabilities of detecting clinical BSE in ambulatory vs. non-ambulatory cattle at antemortem inspection post-January 12, 2004 are a mute point because non-ambulatory cattle are not subjected to antemortem inspection and, if they become non-ambulatory post-antemortem inspection, then they are usually tested for BSE.

The scope of this analysis did not call for us to evaluate scenarios reflecting conditions post January 12, 2004. However, the scenario contemplated by the reviewer is effectively equivalent to assuming that non-ambulatory animals are designated as "clinical" at ante-mortem inspection 100% of the time. Clinical animals may not be sent to rendering or used in human food. Given the limited impact of ante-mortem inspection assumptions on the simulation results (see Section 2.2.2 of Appendix 3A in the 2003 Harvard BSE risk assessment), it is unlikely that this revision would have a substantial impact on the simulation model's predictions. Likewise, results for the Sensitivity 5 scenario in this report indicate that this assumption has a limited impact on the model's predictions.

4c. Analysis of alternative scenarios (Section 2.3.1) in the *USDA 1* condition, and *Sensitivity 5* analysis using the more "pessimistic" robabilities

of inspectors identifying cattle with clinical BSE signs if they are ambulatory vs. non-ambulatory (Section 2.4; 50% and 25%, respectively) cannot possibly reflect reality. Thus, it was difficult for this reviewer to comprehend results of analyses and conclusions generated from Sections 2.3.1 and 2.4. It is possible that the "Downer" policy would reduce risk more than by 2% as concluded.

First, we note that Reviewer #1 criticized our base case assumptions for this parameter as being to optimistic and suggested detection rates in the neighborhood of 50% (see paragraph (e) in those comments). In any case, as we noted in response to comment 4b (above), this assumption does not have an important impact on the results.

5a. With respect to Section 2.2.4 of Methods, it was noteworthy that the investigators attempted to revise Feed Ban Compliance rates given growing amounts of compliance data being available via FDA-CVM. However, the report did not explain why the FDA data from April 2002 only reflected those facilities handling prohibited materials. Feed utilized for the majority of fed cattle is derived from facilities that do not handle prohibited materials; facilities handling prohibited materials may provide feed that is used on farms/ranches for cows/bulls, but distinction among the slaughter populations was not addressed in the model (previously described). Therefore, and without consideration of the distinction in risk associated with the two separate types of slaughter populations, should not the values from all inspected facilities (whether or not they handle prohibited materials) be used?

It is important to understand that the model does not describe where cattle feed comes from. Instead, it describes what happens to cattle tissue after death or slaughter. The fact that the majority of cattle feed comes from facilities that do not handle prohibited feed is not relevant for our purposes. We are concerned with what fraction of cattle tissue will find its way back to facilities that produce cattle feed. For example, if 10 ID_{50}s end up in cattle feed, it is that quantity that drives the extent to which BSE spreads, not the fact that (hypothetically), 99.9% of the feed administered to cattle is completely free of contamination because it was produced in facilities that handle no prohibited material. Admittedly, we assume that although exposure to BSE-contaminated feed depends on feed practices that vary by age and cattle type, the amount of contamination per unit volume of feed is the same across all segments of the cattle population. However, we are unaware of any data that could be used to quantify differences in the extent to which feed might be contaminated (per unit volume) across cattle sub-populations.

5b. Furthermore, it would be useful for the investigators to report the estimated probability that an infective dose of the BSE agent would be transmitted to ruminants as a result of each case of mislabeling and commingling cited by FDA—a citation by FDA does not necessarily translate into contaminated feed that was provided to cattle.

The probability requested by the reviewer depends on the mislabeling or contamination probability for MBM, the disposition of the MBM (is it used for feed production; what kind of feed production facility is it sent to – prohibited, mixed, non-prohibited), the mislabeling and contamination probabilities for feed, and the disposition of the feed (is it used for cattle feed). The model does not calculate the overall probability that a specific mislabeling or contamination episode will translate into BSE exposure among cattle. Instead, this probability is an emergent property of the simulation.

5c. It was not apparent in the report how the "revised worst case" values in Table 2 were computed given the data provided in Table 1.

Numeric columns 1, 2, 4, and 5 (the base case (2003) and worst case (2003) entries) are taken directly from our 2003 risk assessment. The "probability of contamination" and "mislabeling probability" values for columns 3 and 6 (revised worst case) are reproduced from Table 1 – see the shaded values in Table 1. We used the same "proportion of prohibited material transferred to non-prohibited material per contamination event" values as we did for the 2003 worst case scenarios.

5d. Nonetheless, it was noteworthy that the revised worst case probabilities of contamination of feed were dramatically reduced from the 2003 risk assessment.

No response called for.

5e. With respect to analyses conducted in *Sensitivity 1* and *2* (Section 2.4), the pessimistic rates were completely unrealistic with respect to, at a minimum, the fed cattle population.

With the exception of the June 3, 2005 comment from the National Grain and Feed Association (see http://www.ngfa.org/article.asp?article_id=5460), we are unaware of any information to better quantify this parameter. As in our 2003 report, we continue to call for better information to reduce the uncertainty associated with this assumption.

5f. Additionally, further elaboration is needed for readers to comprehend the practical meaning of mislabeling vs. contamination vs. misfeeding and the impact of each on risk as described in the *Sensitivity 1* and *2* analyses; these all tend to result in the same net effect—the feeding of prohibited MBM to cattle, but at differing probabilities of prion transmission.

The results for Sensitivity Analysis 1 (mislabeling and contamination) and Sensitivity Analysis 2 (misfeeding) make this point clear.

6. Section 2.2.5 of Methods should be revised to reflect that bone-in cuts from cattle >30 months of age are potentially important because they may contain dorsal root ganglia (DRG); even for the base case model, spinal cord should not reflect a great risk as it was removed from carcasses prior to December of 2003—albeit less aggressively. Presence of DRG should be the primary concern. The analysis assumes "that for all animals 12 months of age and older, 30% of spinal cord ends up in bone-in beef when the spinal cord is not removed during processing"—the key words here for the base case model are "when the spinal cord is not removed during processing" and it was not clear from the text how often this was projected to occur—were the 30% values intended to reflect "when spinal cord is not removed"? Spinal cord from carcasses of cattle of any age would rarely be expected to enter the food chain at any time, before or after December of 2003 and, hence, this would affect *Sensitivity 4* analysis as well as conclusions regarding conservancy described in 3.1.1.

We cannot understand this comment. Which specific assumption is the reviewer suggesting we change and what is the suggested revised value?

7a. With respect to "Alternative Scenarios" evaluated, this reviewer would prefer to also see reflected in analyses and conclusions a combination of *USDA 1* plus *USDA 2* plus *USDA 3* as that combination reflects regulatory policy since January 12, 2004.

This scenario is beyond the scope of this report. Moreover, the results indicate that when two of the USDA scenarios are combined, there are no synergistic effects.

7b. Likewise, and although not necessarily proposed by FDA (but surely suggested by foreign governments), it would be useful for this study to consider MBM prohibition from all livestock feeds—Section 2.3.3 states that "changes proposed by the International Review Committee" included ("*Int Comm 2*") "Prohibition of all meat and bone meal from ruminant feed" which does not assess removal from all livestock feed.

Consideration of this scenario would require more specific direction. In particular, it is not clear if the reviewer would intend to in effect eliminate all misfeeding (no feed would contain cattle protein). If this is the case, then it is clear, even without use of the model, that the spread of BSE and potential contamination of human food would be virtually eliminated. On the other hand, if inappropriate use of cattle-derived protein is still contemplated, these impacts would persist to some degree.

7c. Lastly, it was not clear in Section 2.3.3 what was meant by the phrase "It is important to note that none of these scenarios remove dead stock from the animal feed chain," and this phrase is used in several locations within the report to qualify model results. Do the authors mean to say that "we have not considered the removal of MBM from feeds provided to all animals"?

The text referenced by the reviewer refers to our assumption that dead stock (animals that die prior to slaughter) may be rendered and hence may be used in feed.

DETAILED TECHNICAL COMMENTS:

- Throughout the text, use of the term "antemortem" is not consistent. In different locations of the report, it is sometimes italicized and sometimes not. It is sometimes provided as two words (e.g., ante mortem), and sometimes as a single word. An abbreviation is sometimes used to reflect the term without initialization of the abbreviation (i.e., AM). The word should be used throughout the report in the form: "*antemortem*."

  All occurrences of ante mortem changed to "*antemortem*" (italicized).

- On P5-6, the sentence: "However, because the ban does not remove dead stock from the animal feed pathway, it brings about only a relatively modest reduction in the average predicted number of new cases of BSE in the 20 years following the introduction the disease" should be revised by adding an "of" following the word "introduction." Concerns about the intended meaning of this sentence were expressed previously in this review.

  Fixed.

- On P6 (last paragraph), the sentence beginning with "Overall, it is clear that . . ." should be revised/reworded; e.g., "Overall, it is clear that by eliminating the most BSE-

infectious tissue from human food, animal feed, or both, specified risk material bans have a substantial impact on potential human exposure."

Fixed.

- On P7 (last paragraph), omit the comma following "December" (this is necessary in several document locations).

  Fixed.

- On P9 (2nd paragraph), the sentence beginning with "The AM inspector follows two sets of . . ." should be revised to insert the words "whether or not" between "governs" (first use) and "an."

  Changed to "… governs whether an animal can be used …".

- On P10 (end of top paragraph), to be consistent, the term "US" should be revised to "U.S."

  Fixed.

- On P14 (1st paragraph), the sentence beginning with "Mislabeling occurs when a producer . . ." should be revised to say "Mislabeling occurs when a feed manufacturer . . ."

  Changed to "Mislabeling occurs when a renderer or feed manufacturer…". Note that the paragraph refers to both rendering and feed production.

- The next sentence "Contamination occurs when a prohibited product crosses over into non-prohibited product" is not accurate. A more precise method for conveying the intended meaning here would be to say that "Contamination occurs when a feed that is not labeled as containing prohibited product is tainted with prohibited product." Incidentally, such contamination can occur in more locations along the feed chain than just at the point of manufacturing.

  Changed to "Contamination occurs when MBM or feed not labeled as containing a prohibited product is tainted with prohibited product."

- The definition for "mixed facilities" (parenthetically) should be revised to say "facilities that manufacture feed containing prohibited product and feed containing non-prohibited product on the same production line." Likewise, the last sentence in this paragraph requires revision.

  Text changed to "(facilities that manufacture product containing prohibited material and product designated as not containing prohibited material on the same production line)"…

- On P15 (2nd paragraph), the sentence "Table 1 reproduces . . ." should be restructured to improve clarity.

  We do not understand what is not clear about this sentence.

- On P17 (1st paragraph following subtitle 2.2.6), the Cohen *et al*. (2003a) citation should reflect past-tense; the word "note" should be revised to say "noted" (the authors use the past-tense further down in the paragraph via the word "described").

  Fixed.

- The sentence ending with "1 in 20,000" in the next paragraph should be revised to say "1 in 20,000 per year."

  We have not made the suggested change. The phrase "1 in 20,000" is a rate (1 animal for every 20,000 slaughtered). Time is irrelevant.

- Lastly, given that a new domestic BSE-positive cow was announced in June 2005 (the "Texas cow"), at a minimum, discussion of prevalence of the disease in the U.S. should reflect the new surveillance program and that new case.

  The Texas case has been incorporated into the discussion.

- On P20 (Sensitivity 6), an additional closing parenthesis is needed following the "Cohen *et al*. (2003a)" citation.

  Fixed.

- Also on this page, should not a portion of the 2nd paragraph following "Results and Discussion" (description of the Ro value newly included in this report) be moved to the Methods section of thepaper (Section 2.1.4)?

  The discussion of R_0 would conceivably be moved to the methodology section. However, we feel that it is best left in the results section. The methodology section focuses on how we have modeled the U.S. agricultural system. The R_0 concept pertains to how we describe the results of that modeling effort. At the very least, the reader not familiar with the concept of R_0 would first encounter its use in the results section and might then have a more difficult time finding its description if that description appeared back in the methodology section among the discussion of the model's assumptions.

- On P21, the subtitle "Base Case with 10 BSE-Infected Animals Introduced:750,00 Trials" should be revised to reflect "750,000 Trials."

  Fixed.

- Also, the last paragraph on this page beginning with "This analysis forms . . ." requires revision to (a) eliminate the word "the" between "subsequent" and "evaluations" and (b) add a space between "version" and "of."

  Fixed.

- On P22 (2nd paragraph), the word "of" between the words "mean" and "estimated" should be omitted.

Fixed.

- On P23 (1st paragraph following "USDA Alternative Scenario 1"), use of the term "fallen stock" is not appropriate (described previously). The intent here is to characterize that "downers" are more likely to have contracted BSE than ambulatory animals, but use of the "fallen stock" term as defined in the report suggests that this sentence actually means "dead" animals are more likely to "have a higher rate of BSE than ambulatory animals . . ."

  Fixed.

- Also on this page, the word "mean" should be inserted into the sentence beginning with "The measure does reduce predicted . . ." between "decreasing the" and "number."

  Fixed.

- On P24 (1st paragraph following subtitle "USDA Alternative Scenario 3"), the term "spinal cord" should be omitted.

  Fixed.

- On P32 (last paragraph), the investigators say that "The International Review Subcommittee convened by Secretary Veneman suggested consideration of a prohibition on use of specified risk material from animals 12 months and older in both human food and animal feed." It is appropriate to point out in this paragraph that, essentially and without regulatory policy requiring it, the U.S. packing industry already eliminates from the human food chain most SRMs from all cattle on a voluntary basis (the only exception to this is vertebral column on some bone-in cuts and a few beef heads from cattle less than 30 months of age).

  While this statement may be true, we would rather not make such a statement without supporting documentation. In any case, the point is not central to the discussion.

- On P33 (last paragraph), the words "(perhaps zero)" should be omitted given the "Texas Cow."

  Fixed.

Response to Reviewer #3

Peer Review #3 of the "Harvard BSE Risk Assessment" (Conducted by Modeler)-mk

This review is organized based upon the questions identified by FSIS as described in "Directions for Peer Reviewers"

a. Evaluate whether the modeling approach adequately meets the goals and tasks outlined in the Statement of Work for the Harvard BSE Risk Assessment

The Harvard BSE Risk Assessment completed the tasks outlined in the Statement of Work. These tasks include: (1) revising the model by updating assumptions in the 2001 Harvard base line scenario to reflect the information available through December 22, 2003; (2) analyzing the effects of the BSE-related policies implemented by U.S. DA and proposed by FDA; (3) analyzing the recommendations of the International Review Subcommittee; (4) providing the technical report. The products and results are provided as specified in the Statement of Work.

The Chapter 2 of the technical report introduces the methods used to complete the tasks. However, in most cases, the Chapter describes how the model assumptions and parameters are revised. No information is provided on how the risk assessment model was developed, how the revisions are modeled, and what sampling techniques are used. For example, what methods are used to propagate the uncertainty in model inputs to model outputs? What components are included in the risk assessment models? How is the human exposure to BSE modeled? What approaches are used to develop the model? Without this information, it is not possible for reviewers to evaluate whether or not the modeling approach adequately meets goals and tasks.

There is a fundamental problem with using a model for policy analysis by a public agency when that model is inadequately documented in a manner that is accessible to peers. It is not the reviewer's job to guess at what was done. It is the authors' responsibility to clearly document the model in terms of the following:

- what are the requirements for the model, including spatial and temporal scales/resolution, subpopulations of interest, exposure pathways and routes, etc. – i.e. what are the scenarios and their key characteristics.
- Based on the scenarios to be analyzed, what are the boundaries of the models – i.e. what spatial extent, time frame, subpopulations, etc, are included in the model? How does the domain of the model compare with the desired coverage of the scenarios of interest? Are there any uncertainties associated with inability to fully capture key aspects of the scenarios within the modeling framework?
- What are the key analytical equations for each major component of the model? What is the basis for each? What are the key choices regarding the structure of the model that might introduce or deal with structural uncertainties?
- What are the interfaces between components of the model?
- What are the key inputs to the model and their input assumptions, whether point estimate or probability distribution? What is the basis for each?

The report evaluated by the reviewer states in the first sentence of the methodology that this analysis was conducted by making modifications to the Harvard simulation model developed for earlier analyses. That sentence cites two sources, one of which is our 2003 risk assessment.

That document, which is available on the internet (citation provided in our report), addresses the questions raised by this reviewer.

b. ***Review the available data and underlying assumptions used in this Risk Assessment***

This is beyond the scope of our review.

No response called for.

c. ***Review whether the revised model adequately characterizes the uncertainty distribution of the potential human exposure for the regulatory analyses.***

Without adequate documentation of the model and its input assumptions, this question cannot be answered.

See response to (a).

d. ***Are the effects of BSE-related policies implemented by USDA and proposed by Food Drug and Administrations (FDA) of since December 23,2003 adequately modeled and evaluated***

See response to c.

See response to (a).

e. ***Are the recommendations of the international Review Subcommittee adequately modeled and evaluated.***

See response to c.

See response to (a).

f. ***Review if adequate documentation has been provided for files (used and generated) and within source codes***

The source codes and accompanying software model provided in the CD are reviewed. We noticed that there is a "Readme" file introducing the contents of the CD. However, we did not find other documents to describe the software model and how to use the tool. The following questions are identified during the review process and needed to be addressed.

1. No user manual is found in the CD to introduce the use of the software model. It is necessary to provide a user manual to guide users to install the software onto users' local machines and to help users to run the model. The document should clearly state the operating or support environment to run the software model, how to use it, and trouble shooting measures.

   Providing extensive user documentation, such as would be developed for commercially available software, was never within the scope of any work conducted by Harvard for USDA. However, Harvard has provided documentation of the model in our 2003 risk assessment (see response to (a)) and the DATA FILE DOCUMENTATION file mentioned by the reviewer.

We do not understand the reviewer's comment that the documentation does not explain how to install and run the software. Page 1 of the Data File Documentation provides an example describing where to put the executable, where to put the parameter files, and how to execute the program.

2. No documents introducing the files contained in the "Batch Runs" folder. Also, no document and comments are provided regarding how to change the parameters if users want to run new scenarios. Without a user manual and those documents, it is hard for users or reviewers to duplicate the results and make new simulations.

   See response to comment (f1). We do not understand the comment stating that thee is no documentation describing how to change the parameter files. The Data File Documentation explains that the parameter files are in ASCII format, from which it follows that any ASCII editor can be used.

3. Although some documents or comments are provided in the source code, these are not enough. There are many of C++ source code files, however, there are no documents that describe the structure design of the software model and the logical relationships among the different C++ class files. For some source code files, no comments are provided. Because there is lack of comments within the C++ source codes and no document describing the relationship among the the C++ source files, it is almost impossible for users to add or modify the source codes. Maybe only the original developers of the model could easily add or modify source codes for the current version. Therefore, it is necessary to provide a document describing the structure design of model and logical relationships among different components and enough comments within sources codes.

Based upon the above information, it is the reviewer's opinion that there is not adequate documentation provided for the files contained in the CD and within source code.

With the exception of some low level utility functions, the code is documented. In any case the appropriate level of documentation depends on the needs of any particular user. The reviewer notes that "…only the original developers of the model could easily add or modify source codes for the current version." Any user interested in modifying the original code would almost certainly have to spend more time examining it and the background material (including the 2003 risk assessment that explains the overall structure of the model) than it seems was within the scope of the task for this reviewer.

g. Adequate sensitivity analysis has been provided for the new baseline case

The authors conducted the sensitivity analysis based upon the new baseline case scenario to explore the impact of by using alternative assumptions for the specific parameters and ante mortem inspection process. Six case study scenarios were designed to identify the potential impacts of using different values for those assumptions on the predicted number of additional new case of BSE over 20 years and total human exposure to BSE-contaminated food. However, the report provided by the authors does not have the following information:

1. How did they perform the sensitivity analysis? What sampling approach did they use to change the values?

We have revised the introduction to Section 2.4 to better describe the sensitivity analysis. As the text explains, we have investigated the impact of alternative pessimistic assumptions. That is, we set each uncertain assumption to be analyzed to a pessimistic value while holding other assumptions to their base case values and then re-ran the simulation. Therefore, no sampling was used to change the parameter values.

2. What sensitivity analysis methods did they use to conduct the sensitivity analysis? Why are those sensitivity analysis methods used? The selection of sensitivity analysis methods depend on the model characteristics, the objectives of the analysis and other factors. The use of improper methods may produce incorrect results and thus lead to wrong policy implications. Thus, it is necessary to provide such information in the report.

   The revised text at the beginning of Section 2.4 describes our approach and the rationale.

3. In the introduction to the sensitivity analysis studies as described on page 20, the changes for main variables are made from one value to another value, for example, increasing contamination rates to 14% (MBM production) and 16% (feed production). The questions arise here: (1) what are reasons for specifying the new values? (2) Is it true that the new values just replaced old ones, and then new results were obtained? If so, we think that such analysis should be called as "worst case study" or a "bounding analysis" and not a "sensitivity analysis" (If the authors think that the new values are the worst case). Isn't it possible that, for example, contamination rates will fall within the old value and new one? The sensitivity analysis is to assess how variations in a model input affect on the model output; basically the variations change randomly over a range or follow a distribution (In this case, a uniform distribution may be a good assumption).

   In response to question (1) – Our report states that the 14% worst case contamination rate for MBM production and 16% worst case contamination rate for feed production are taken from Harvard's 2003 risk assessment. Documentation for those values appears there. We do not know what other assumptions the reviewer believes to be inadequately documented.

   In response to question (2) – Our understanding of the term "sensitivity analysis" is not consistent with the reviewer's claim that it must assess the impact of random changes in an assumption's value (drawn from a probability distribution). For example, see Figure 2 in Kuehne et al., "Treatment for hepatitis C virus in human immunodeficiency virus-infected patients" *Arch Intern Med*. 162:2545-2556. See also comment (2) in Section 9.1 of the October 31, 2002 peer review of the original Harvard BSE risk assessment (available at http://www.aphis.usda.gov/lpa/issues/bse/BSE_Peer_Review.pdf).

Without above information, it is hard for reviewers to determine whether or not the sensitivity analysis conducted on the new baseline is adequate.

See responses above.

Response to Reviewer #4

Peer Review #4 of:

Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update – Phase IA

Overview of Peer Review Scope

Materials Provided for Review

A CD dated July 26, 2005 containing:

> *Report entitled, "Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update Phase IA" (dated June 1, 2005).*
>
> *Source Code (approximately 95 files of C++ code and related files).*
>
> *Compiled application <madcow.exe>, together with various support files (*.bat files for setting up batch runs and data control files).*

Also consulted:

> *Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States, revised October, 2003.*
>
> *Response to Reviewer Comments, October 2003.*

Scope of Review

This review is focused on the mathematical, computational and implementation aspects of the risk assessment model and the corresponding impacts on results and conclusions. The reviewer is not an expert in the scientific assumptions that underlie the risk assessment.

Response to Charge Questions

Evaluate whether the modeling approach adequately meets the goals and tasks outlined in the Statement of Work for the Harvard BSE Risk Assessment.

Overall, the modeling approach taken represents an appropriate design to achieve the goals of the Statement of Work. The modeling approach is that of an explicit, discrete-event model which allows for detailed treatment of time-sensitive phenomena, very specific treatment of risk management interventions and discovery of important (and unimportant) phenomena in the system being characterized.

The design of such a model ultimately requires some compromise. With respect to the goals in the statement of work, it appears that the requirement for uncertainty distributions has not been met (section 1.H.v). This is addressed in 2.3 below. Concerns for the adequacy of the numerical stability are described in Section 2.7 below.

No response called for here. See responses to comments 2.3 and 2.7 below.

Review the available data and underlying assumptions used in the Risk Assessment.

As stated above, the reviewer is not an expert in the scientific data and the basis for the underlying assumptions. The computational implementation of the assumptions appears to be sound, subject to limitations cited elsewhere in this review.

No response called for.

Review whether the revised model adequately characterizes the uncertainty distribution of the potential human exposure for the regulatory analyses.

Requirement 1.H.v in the Statement of Work states, "*Uncertainty distributions that reflect stochastic occurrences for assumed fixed model parameters and uncertainties about those parameter values.*"

This requirement appears to be met with respect to stochastic occurrences, but the distributions presented do not include uncertainty with respect to parameter values. The model and the report do provide distributions for stochastic variability within the set of fixed model parameter assumptions. However, it needs to be made very clear to the reader that the model and the report do not provide uncertainty distributions, in the sense of epistemic uncertainty.

One might safely assume that a majority of readers (including risk management personnel) will not be aware that the dispersion that is carefully documented and presented is derived only from the stochastic variability that stems from a set of fixed model assumptions about an inherently stochastic system. In the absence of this understanding, it will be very tempting to assume that a statement (e.g., that the 95%ile for R_0 is X) represents a statement of confidence with respect to the epistemic uncertainty.

If fully quantified across all parameter estimates and including the considerable model uncertainty that stems from fundamental epistemic uncertainties, the total uncertainty in any estimate or statistic would be considerably larger (possibly orders of magnitude larger) than the stochastic variability that is presented. To respect this reality, and in the absence of quantitative estimates of uncertainty, a clear qualitative statement and discussion of total uncertainty is required to adequately address this issue. The model's authors should not rely on the reader's ability to surmise the overall level of uncertainty that might be inferred by the numerous statements about uncertainty in individual parameters, particularly when presented with hundreds of tables and graphs showing only stochastic variability that may be mistaken for uncertainty. In addition the reader of the updated risk assessment report is further divorced from the total uncertainty since most of the epistemic issues are discussed in the prior report.

Arguably, the stochastic variability is of relatively little interest to risk management when compared to the total uncertainty in estimates of risk or risk reduction. Accordingly, it should be made clear to the risk managers, regulatory analysts and other readers of the report that it is not appropriate to apply the quantitative estimates of stochastic variability as surrogates for the total uncertainty in the estimates of risk or risk reduction benefits, as might be required in regulatory analysis. This would represent a considerable underestimate of uncertainty and would undermine the modeling effort considerably through misuse of the results.

We have added a paragraph at the beginning of Section 3 (results) to clarify the distinction between the stochastic variation characterized in the output distributions that appear in Appendix 2 and the uncertainty arising from differences in underlying assumptions (see text "The graphs and tables in Appendix 2…").

Are the effects of BSE-related policies implemented by USDA and proposed by FDA since December 23, 2003 adequately modeled and evaluated?

A key benefit of the design of the model is the ability to explicitly model the potential impact of risk mitigations. This appears to have been adequately modeled and evaluated subject to the quality of the assumptions underlying their impact on parameter estimates. This determination of validity is not within the scope of the reviewer's expertise.

Statements about the overall characterization of uncertainty in 2.3 apply to the evaluation of these policies. Given that these policies are the subject of regulatory analyses, the need to adequately characterize the epistemic uncertainty, even if only qualitatively, is particularly important.

No response called for.

Are the recommendations of the International Review Subcommittee adequately modeled and evaluated?

Similarly to 2.4, these recommendations appear to have been adequately modeled and evaluated, subject to the validity of the assumptions underlying the impact on model parameters. This determination of validity is not within the scope of the reviewer's expertise.

Statements about the overall characterization of uncertainty in 2.3 apply to the evaluation of these policies.

No response called for.

Review if adequate documentation has been provided for files (used and generated) and within source codes.

This issue presents a difficult determination since no uniform standard of adequacy exists and the charge to reviewers does not provide an indication of what criteria apply in determining adequacy in documentation. The reviewer notes that the level of documentation is not specified in the Statement of Work, beyond requiring a technical report and an executive summary.

The reviewer may selfishly apply a standard of adequacy which is largely based on whether they had sufficient time, resources and specific expertise in the modeling technology (software environments, programming languages, etc.) in order to adequately understand the implementation of the model within the scope of the review process. From this limited perspective, the documentation is quite inadequate.

At another extreme, one might consider whether the model is sufficiently documented such that a knowledgeable investigator, who is (or has access to resources with) fluency in the C++ programming language and has considerable time and incentive to trace the inner workings of the computer program across multiple source code files, could gain a sufficient understanding of the model such that they might use and adapt the model. This would appear to be the audience that the authors had in mind when referring to the adequacy of the documentation for "interested investigators" in their response to a previous round of peer review comments (p. 23). From this second limited perspective, the documentation would presumably be adequate.

From a broader perspective, and presumably closer to the perspective which is intended by FSIS in the charge to reviewers, the documentation is not adequate. There are a number of specific limitations to the documentation which, if addressed, would bring the model closer to a broadly, though admittedly subjectively, acceptable level.

a) The overall report is now structured as two distinct documents, the original report and the update. The latter, strictly speaking, is the subject of this review. While this may be convenient for the authors and for the few people who have maintained an awareness of the content of the original report, review of the report really requires reading both texts. This realization may suggest rethinking the overall documentation structure.

b) The original report is the basis for actually understanding the model. The reader's ability to follow the model would be greatly facilitated by a detailed flow-diagram of the disposition of the various objects in the discrete event system (at least for the life cycle of a few herd-lifetimes). If this diagram contained 'tags' which led the technical reader to the appropriate C++ source code file and datafile, then the overall task of reviewing the model implementation would be considerably more realistic. Without such a diagram, it is incumbent upon the reviewer to create a mental map between the textual discussion of the discrete-event simulation in section 3 of the original report, changes to the simulation model described in the updated report, and the over 90 C++ source code files which constitute the model code. The lack of a 'roadmap' is the greatest single threat to the adequacy of the documentation.

c) The documentation of the model and its results seems to be thorough at two extremes. The overall context of the model, the high-level discussion of the discrete-event system, the risk mitigations, and the high-level conclusions are well presented across the two reports. At the other extreme, hundreds of tables and graphs are presented for each scenario so that the interested reader can carefully scrutinize the results. What seems to be lacking is the combination of text and exhibits to provide a mid-level discussion of the model with reference to specific tables or graphs of results (as opposed to reference to an entire section of an appendix). A meso-scopic view (as opposed to the thorough macroscopic and microscopic views) of the model would be very valuable with respect to the technical discussion of the model, and the readers' ability to appreciate the model. A professional technical writer may serve this purpose well.

d) Although the source code, data files and batch-run files were provided, it is not apparent what is required to run the model. Given the considerable computational burden, it would be helpful if some indication was provided as to how long the computation might take, or some minimal indication of progress so that a user might know when to expect the simulation to finish. It would also be useful to have some suggestions for what sort of computational power might be appropriate for the task (memory, hard drive, processor speed, etc.).

e) The C++ code is what might be called, 'minimally documented'. [To provide some context, an excerpt of the source code with in-line documentation is provided below for readers of the review]. As a non-expert in C++, but with some experience and familiarity with object-oriented programming, the documentation is not adequate. It is not clear to this reviewer what level of documentation would be required by someone with a true working knowledge of the C++ programming language since some of the workings of the model would be somewhat more apparent to those truly fluent in C++. At the other extreme, considering someone who has no experience of object-oriented programming, it is not clear whether any level of further documentation within the source code can usefully replace that knowledge. As such, the reviewer is unable to come to a conclusion on the appropriate level of documentation for the source code, particularly when the audience of the documentation is not specified. One might consider documentation standards put forth by the community of software engineers, but whether that would be the reasonable standard in this circumstance is a matter of judgement since no standard of reasonableness has been asserted by FSIS.

Excerpt from C++ source code file: <bloodInfector.cpp>. [Line breaks and spacing in the text have been adjusted slightly to fit this pagination.]

```
//Distributes infectivity from blood meal among members of herd and creates the resulting infected bovines.
void BloodInfector::visit(BovineHerd* herd) {

        curTarget = 0;
        std::vector<BovineHerd::iterator> selected;
                //Vector of BovineGroups with numTargets entries, one for each

        //exposed bovine.  Note -- a BovineGroup can appear multiple times in this vector.
        double (*weight)(BovineGroup const&) =  //weight function retrieves the consumption weight for
bovineGroup
                BloodConsumptionAdapter;

        selected = KHD_UTIL::PoissonSelectMulti                 //Get the list of bovineGroups containing exposed
bovines.
                        (herd->begin(), herd->end(), weight, numTarget);

        std::vector<BovineHerd::iterator>::                     //Iterator and end marker for vector of
bovineGroups with exposed
                iterator it, end;                               //bovines
        end = selected.end();
        for(it = selected.begin();                              //Iterate through vector of selected bovineGroups
                it != end; ++it) {
                (*it)->accept(*this);           //BovineGroup accepts the proteinInfector, which then visits it
                curTarget++;
        }

        numTarget = 0;
        curTarget = 0;
```

}

We agree with the reviewer that better documentation of the source code would be helpful. The specific suggestions provided are good ideas. However, developing that level of documentation is labor intensive and was not within the scope of either this project or any of the previous efforts conducted by Harvard on behalf of USDA.

That being said, we do believe that available reports do provide an adequate description of the model's overall function (*e.g.*, see Figures 3-1, 3-2, and 3-7 and associated text in Harvard's October, 2003 assessment). It is our impression that the majority of models in the peer reviewed literature are not even made available to the public. Looking at the Harvard model within this context, it seems that the Harvard simulation model is not outside of the main stream in terms of its accessibility.

Review if adequate sensitivity analysis has been provided for the new baseline case.

One key element of sensitivity analysis is the sensitivity of the discrete event model to the number of iterations. The report and the statement of work report on a failure to achieve adequate convergence for upper percentiles of the distribution ("Work Temporarily Curtailed") in a first iteration of the new baseline. By extension, this is presumed to be the case for the previous (2003) report. The recent Statement of Work suggests that the model should achieve stable estimates at "high (e.g. 99.5^{th}) percentiles."

The reader of the report is unable to determine the extent of the problem that underlies the need for such a drastic increase in the number of iterations. The previous results were based on the order of 1000-5000 iterations. The new simulation specifications call for millions of iterations (when measured by the number of animals introduced). This raises a number of concerns.

The reviewer's comment seems to imply that adequacy of numerical precision is a property of the simulation alone. That is not the case. It also depends on which output the risk manager is interested in and what level of precision the risk manager requires. Therefore, it does not follow that because much less numerical precision was achieved in the analyses for our 2003 report than in the current report that the numerical precision of those earlier analyses were inadequate. The present analysis was conducted to precisely quantify the impact of specific interventions. Because their impact was in some cases small, the level of precision needed to quantify their impact was substantial. In contrast, the October, 2003 analysis was more exploratory in nature, addressing qualitative issues, such as 1) whether BSE would spread substantially if introduced into the U.S.; and 2) identifying the main sources of potential human exposure to BSE. With regard to the first issue, we were able to show with a high degree of (numerical) confidence that the number of cases would decline over time (suggesting $R_0 < 1$) and hence establish that there would not be an epidemic like that experienced in the UK. With regard to the second issue, we were able to identify AMR and brain as the largest contributors to human exposure. In short, there was no "problem" with the October, 2003 report. A greater level of precision was needed for the present analysis because the questions asked changed.

The 2003 report and the response to comments indicated a clear lack of concern on the part of the authors with the adequacy of the number of iterations. The 2003 report contained a very brief appendix (#4) which describes how percentiles were calculated, but did not provide a conclusion with respect to the adequacy of numerical stability. The author's response to previous peer review

comments provided assurances that the numerical stability (for 1000, 5000 and in one case 780 iterations) is sufficient for the purposes (p. 17).

> Rather than telling the reader what level of precision is sufficient, we reported our results and also quantified the degree of numerical imprecision. From that information, the reader can decide if we had sufficient precision to justify our conclusions. To use a metaphor, we reported the probability of a Type I error without establishing an ex ante standard for statistical significance. Even though we did not establish an ex ante standard, the results were sufficiently precise for our purposes in the sense that they support our qualitative findings with a high degree of certainty. For example, we estimated that 4.25 cattle would become newly infected in the 20 years following the introduction of 10 infected cattle into the U.S. The upper bound of the 95% confidence interval for this statistic is 4.75 (see Table 1 in Appendix 4 of our October, 2003 report. Even this upper bound value is well below what one would expect if $R_0 > 1$. Hence, we established with a high degree of confidence that BSE would not spread rapidly (as it had in the UK) following introduction into the U.S. Likewise, numerical precision for estimated potential total human exposure was sufficient to establish that the exposure would be many orders of magnitude less than it had been in the UK.

The current updated report, having increased the number of iterations by a factor of 2,500, provides a one paragraph technical appendix which references a SAS procedure, and again, no conclusion with respect to the adequacy of numerical stability. Furthermore, the percentiles that are presented include up to the 95th percentile, but not the 99.5th as suggested in the statement of work.

> We note first that the statement of work does not mandate reporting of results at this percentile, but lists it only as an example. Moreover, it calls for Harvard to explore this issue. The language for this requirement is open-ended and, although the reviewer could not have known, USDA and Harvard agreed to limit attention to no greater than the 95th percentile during meetings subsequent to the drafting of the statement of work.

It is important that the situation with respect to numerical stability for both the findings in the original report (2003) and the current report be resolved and clarified. The reader is left with the following questions:

a) Given that the current report requires millions of iterations, what proportion of the findings in the 2003 report remain valid or current?

> See response above.

b) What level of stability is sought by FSIS/Harvard and why? How was the number of iterations determined to be 2.5 million?

> USDA told Harvard that 750,000 simulation trials per scenario would achieve precision sufficient for their purposes, assuming 10 animals were introduced per trial. We demonstrated that the level of precision for the mean depended on the product of the number of simulation trials and the number of animals introduced per trial. By scaling up the number of animals introduced by a factor of 50 (to 500) and scaling down the number of trials by a factor of 15 (to 50,000 per scenario), we therefore more than maintained the requisite level of precision. (Note that the product of 50,000 trials and 500 animals per trial is 2.5 million infected cattle.) Moreover, because of the simulation's operation, this

combination of trials and animals introduced per trial could run far more quickly. Because post-processing time (*i.e.*, time needed to read ascii output files and create tables and graphs) depends only on the number of trials and not on the number of infected animals introduced, this approach saved a substantial amount of preparation time.

c) How are conclusions with respect to sensitivity analysis (which are used to limit the scope of subsequent discussion and are used as the basis for subsequent scenario analysis) impacted by the concerns with numerical stability?

As stated above, we did not establish the precision criteria for USDA. Nor did we establish ex ante criteria by which we evaluated the findings for our own purposes. However, it is clear from the results in Appendix 3 that sufficient precision was achieved to support our qualitative conclusions. If there are any conclusions for which this does not appear to be the case, we would like to know.

d) Given that some simulations reported in the 2003 report took 250 hours to run at iterations on the order of 1000s, how long would it take to run a simulation with 2.5 million cattle?

As mentioned in our response to (b), execution time is not a linear function of the number of infected cattle introduced. Instead, it is much more sensitive to the total number of trials. One scenario (50,000 trials, 500 infected animals introduced per trial) takes approximately 3 days on a 2.8 GHz IBM ThinkCentre.

e) With this computational burden, does this reality practically rule out quantitative uncertainty analysis and significantly limit the scope of sensitivity and scenario analysis to perhaps just a pair of scenarios?

The 19 scenarios described in this report take approximately three weeks to run on a set of three simulation machines (total cost of all three machines was approximately $2,500). While processing is time-consuming, it is not impractical.

f) What sort of conclusion might one erroneously draw by relying on only 1,000 iterations, 100,000 iterations, etc.?

As explained earlier, whether the conclusion is erroneous depends on the question being asked. We have reported the numerical precision of our estimates. In neither this report, nor in our October, 2003 report, does this reviewer identify an example of precision insufficient to support any of the conclusions drawn in our report.

Given that this is a fundamental question resulting in a significant change in the simulation strategy, more attention needs to be paid to describing this situation with both narrative and quantitative demonstration of stability. This should be prefaced by a statement of what constitutes numerical stability for the specific purposes of this assessment. Clarity regarding the validity of previous conclusions (2003) based on a small fraction of these iterations should be addressed.

As noted above, the change in simulation strategy was driven by a change in the type of question being asked. Hence, the change in strategy does not call into question our 2003 conclusions. Finally, we do not agree with the reviewer's suggestion that we must advance a standard for numerical precision. We have described how precise our results are and have provided the reader with sufficient information to judge whether he or she believes our results to be supported.

Selected Overview Comments

Conservatism – at various points in the text, there are statements regarding the degree of conservatism in assumptions. For instance, (p. 13), "We conservatively assume …". The imbedding of conservative assumptions leaves the results of the report somewhat 'ungrounded' on the continuum between pessimistic and optimistic analyses. Should the reader assume that the net result of several conservative assumptions makes for a conservative estimate of risk? Why were conservative assumptions chosen, rather than a best estimate? Given that there are no statements of global uncertainty in the conclusions, the reader is left to speculate on the position of risk assessment within this important continuum.

Normative Language – the authors should be cautious about the choice of qualifying words in the risk assessment document. At various points, there are references such as "small risk in absolute terms," or that an estimate increases "only slightly." While the current document is relatively tame in that regard, the October 2003 report (which must be understood to digest the updated report) contains numerous instances of language which is pre-emptive of the reader's (in particular, the risk manager's) determination of the level of risk. Examples include use of the terms "extremely unlikely" or "strongly resistant." The authors, having gone to the considerable effort of producing numerical estimates of risk, would be better served by reporting these numbers and avoiding the value-laden and arbitrary terminology.

We have added text to the introduction of Section 2 (Methodology) ("Note that where possible, our base case") explaining that in a few limited cases, we have used assumptions that are "conservative", rather than representing central estimates. The text explains that these assumptions were made when it was not possible to develop central estimates, that we chose conservative assumptions so as to protect the validity of our overall finding that BSE would not pose a substantial risk if introduced into the U.S., and finally that the assumptions treated in this manner are known not to have a substantial impact on the results.

End of review

Comments on the

Harvard Risk Assessment

of Bovine Spongiform Encephalopathy

Update of June 1, 2005

By:

APHIS

FSIS

FDA

APHIS

In addition to specific comments provided below, some general comments about language and/or style in the written report are also included.

(a) Evaluate whether the modeling approach adequately meets the goals and the tasks outlined in the Statement of Work for the Harvard BSE Risk Assessment:
It appears that the modeling approach does meet the goals and tasks outlined in the Statement of Work.

No response called for.

(b) Review the available data and underlying assumptions used in this Risk Assessment.
Please see the details below that address comments on assumptions, parameters, and references.

See below.

(c) Review whether the revised model adequately characterizes the uncertainty distribution of the potential human exposure for the regulatory analyses.
No specific comments.

No response called for.

(d) Are the effects of BSE-related policies implemented by USDA and proposed by FDA since December 23, 2003 adequately modeled and evaluated?
Please see the details below that address comments on assumptions, parameters, and references. It is difficult to evaluate the modeling related to non-ambulatory animals due to the lack of clarity in the assumptions and parameters for this issue.

See below.

(e) Are the recommendations of the International Review Subcommittee adequately modeled and evaluated.
Please see the details below that address comments on assumptions, parameters, and references

See below.

(f) Review if adequate documentation has been provided for files (used and generated) and within source codes
Not evaluated.

No response called for.

(g) Adequate sensitivity analysis have been provided for the new baseline case.
No specific comments.

No response called for.

Comments on language and/or style:

(1) The report uses different language in various sections to describe actions related to feed regulations that were evaluated. It needs to be consistent in the description of the action evaluated. The recommendation from the International Review Team (IRT) was for the removal of all animal protein (mammalian and avian) from ruminant feed. In some instances, this is described more accurately (i.e., page 26 – "ban on any MBM to ruminant feed"). In other instances, it is described as the "removal of all animal protein from animal feed" – which is a completely different action that would have significantly different effects. For accuracy and consistency, this should always be described as a ban on any animal protein (or any MBM) in ruminant feed.

The report has been revised to make the language more consistent. We have also revised the assumptions for this scenario to more accurately reflect the language of the international committee (see description in report Section 2.3.3).

(2) In several places, the report references FDA "proposed rules" or "proposed changes". For example, the following sentence is found on page 7: "The Food and Drug Administration (FDA) also proposed new rules to help prevent the spread of BSE among cattle through contaminated animal feed." This is unclear and can be easily misinterpreted. Readers that are familiar with the federal government rulemaking process could interpret this to mean that FDA has published in the Federal Register a proposed change to the feed regulations – which is not true. FDA has made public statements in various venues committing to consider different changes to the regulations, and it is anticipated that they will publish a formal proposal in the near future. A similar phrase is in the next paragraph (".. or proposed by either FDA or the International Review Subcommittee ….) and again on page 8, and these also need to be changed to more accurately reflect what has or has not been formally proposed as part of the regulatory process.

Fixed.

(3) Page 7, 2nd paragraph – the first sentence references "the potential for humans to be exposed to contaminated meat." This implies that muscle meat is the risky product. The risk, however, is through other tissues. Suggested alternative wording could be "the potential for humans to be exposed to the infectious agent" or "the potential for humans to be exposed to contaminated cattle products".

We disagree. We are referring to muscle meat that is contaminated with the BSE agent. For example, when the carcass is split, BSE agent in the spinal column can end up in muscle meat. It is therefore accurate to refer to it as "contaminated muscle meat." In fact, it would be inaccurate to say that the muscle meat is not contaminated.

(4) Page 13 – "Assuming an incubation period of 36 months, which has been typical in the pathogenesis study, we estimate total infectivity in an animal to be approximately 250 cattle oral ID_{50s} (see Cohen et al. (2003a))." In the 2001/2003 versions of the model, the total infectivity per animal was assumed to be 10,000 ID_{50s}. If this (250 ID_{50s}) is a typographical error, it should be corrected. If something else was meant, it should be fully explained.

The text has been changed to, "Assuming an incubation period of 36 months, which has been typical in the pathogenesis study, we estimate that at 10 months post infection

(when non-zero infectivity in tonsils was observed), total infectivity in an animal to be approximately 250 cattle oral ID_{50}s (see Cohen *et al.* (2003a)).”

Comments about assumptions, parameters, references:

2.1.2 Operation of the Ante Mortem Inspector
The changes to this parameter that reference “allowed use of the animal” are somewhat unclear. It appears that the AM inspector parameter can dictate whether an animal can be used in animal feed, with the parameter set such that if an animal exhibits clinical signs of BSE it will be excluded from animal feed. Currently, there is no requirement for exclusion of such animals from animal feed. In fact, the vast majority of animals condemned on ante-mortem inspection are sent to rendering facilities, and the resulting protein is incorporated into animal feed.

For the purpose of the model, animals discovered at ante mortem as having signs of clinical disease are effectively banned from feed. Recall that only animals infected with BSE are explicitly modeled by the simulation. We assume that these animals can show signs only if they reach the clinical stage of the disease. In the real world, such animals would be tested, their BSE status would be discovered, and the carcass would be destroyed. Hence, for all practical purposes, animals with clinical BSE signs that are discovered by the ante mortem inspector are not allowed to be used in feed. The text has been revised to more accurately explain this issue.

2.2.1 Assignment of ambulatory status
The reference to the APHIS NAHMS survey is unclear and perhaps incorrect. There have been no specific considerations of non-ambulatory animals in NAHMS surveys. APHIS is working with NASS on a study of non-ambulatory animals, and as part of this work NASS released some initial data in May 2005. This would be a more accurate and appropriate reference.

This section has been completely redrafted in response to comments from Reviewer #2. Because other import data are not available, it is not possible to estimate the probabilities described in this section. We therefore address these parameters using sensitivity analysis (see sensitivity analyses #7 and #8). As it turns out, these parameters have a very limited impact on the model’s predictions.

2.2.2 Ante Mortem Inspection
This section is difficult to interpret or understand, and therefore is difficult to evaluate. I believe the primary point of confusion relates to the assumed distinction between clinical signs of BSE and ambulatory status. In reality, ambulatory status – ataxia, hind-limb weakness, recumbency, etc.. - often times is a clinical sign of BSE. While the basic premise of what is being modeled is understood, the assumptions and parameters are not clearly explained. A flow chart with better explanations could be helpful on this point.

Because we no longer develop the calculations (the data needed are not available (see response to comment 2.2.1), we do not believe revisions suggested here are warranted. However, we are not exactly sure what the commenter is requesting.

As mentioned previously, there is also a newly assigned parameter that causes the ante-mortem inspection determination to direct what may or may not be used in animal feed. No explanation is given as to why this parameter has been added, nor what regulations form the basis for this assumption. Currently, there are no restrictions on the use of carcasses of animals condemned on

ante-mortem inspection in the production of animal feed. This parameter should be removed to help ensure the most accurate model of the US industry.

Removal of this parameter is not warranted. There must be some way to destroy animals that are discovered to have BSE through actions initiated by the ante mortem inspector. See also our response to comment 2.1.2.

2.3.3. Changes Proposed by the International Review Committee

It is stated that "none of these scenarios remove dead stock from the animal feed chain", with no explanation as to why such an assumption was made. The usual understanding when discussing regulations that dictate the removal of SRMs from animal feed is that these also apply to dead stock. Specifically, such regulations would require that any deadstock or rendering facility must also remove SRMs from carcasses prior to processing. If these were not removed, then the resulting MBM would not be allowed for use in animal feed. Regulations would not be promulgated that prohibited SRMs derived from animals presented at slaughter from going into the rendering chain, yet allowed SRMs derived from animals that died otherwise to be incorporated into rendered product. This concept should be more accurately reflected in the model, as it otherwise presents a very misleading picture of the reality of such regulations. If it can not be reflected in the model, the reasons should be clearly explained and a more detailed explanation should be provided to ensure the reader's complete understanding.

Fixed as directed. The model has been revised so that the SRM inspector operates on dead animals, as well as on animals sent to slaughter.

3.2.2. FDA Alternative Scenario 1

In this scenario, it was assumed that the only infectivity in blood would be from micro-emboli produced due to the stunning process. However, the Harvard 2001/2003 model also included an assumption of some infectivity present in blood just at or below the level of detection. Research has demonstrated the transmission of BSE in sheep via transfusion. Although these findings can not automatically be extrapolated to BSE in cattle, it would be helpful to maintain consistency with earlier models and consider some small amount of infectivity in addition to that associated with the stunning process.

The 2003 analysis assumed zero infectivity in blood in the base case. Only in one of the worst case scenarios do we assume (even without the contribution from emboli) that the BSE agent can be found in blood. At this level blood accounts for less than 1% of the risk of BSE infection. See Table 3-1 and Section 3.2.2.1 in our 2003 report.

FSIS

Office of International Affairs

We have reviewed the new draft Harvard Risk Assessment, and have a few editorial comments, as follows:

* Page 4, paragraph 2, 1st sentence - the sentence seems incomplete.

The text "Results indicate that… 10, or 50)." is a complete sentence. Note that "scaled" is the verb for the subject ("mean"), i.e., the sentence is

"The mean scaled by the ratio." If there were a comma before "scaled", then "scaled by the ratio…" would be a parenthetical, and the sentence would be incomplete.

* Page 5, paragraph 2, 4th sentence - the word "only" seems to be misplaced.

The sentence is correct as is. We do not see what alternative placement would be superior.

* Page 33, paragraph 2, 1st sentence - the word "Iler" in "...if Iler exposure lead to longer..." seems to be a typo.

Fixed – changed to "smaller".

Office of Policy, Program and Employee Development

Page 32, section 44 -- Conclusion. There must be clarification provided to explain the USDA mitigation effects. First, on the non-ambulatory disabled cattle issue, what I think you need to say is that the removal of such cattle from the human food and animal feed supply is realized simply by ensuring that cattle parts (including SRMs) younger than 30 months that may have BSE are eliminated because the SRMs from cattle 30 months of age and older already are prohibited.

The prohibition against using certain tissues in human food is independent of actions (through *antemortem* inspection) that prohibit the use of entire animals from use in human food. Preventing use of certain tissues ensures that high risk tissues don't end up in human food, regardless of the animal's apparent risk at slaughter. On the other hand, preventing use of high risk animals in human food (*e.g.* nonambulatory animals) prevents human exposure to even those tissues that have low (but not necessarily zero) infectivity.

In addition, in this paragraph, you must clarify the sentence beginning with "Alone, prohibiting" by inserting the following phrase contained in brackets: "Alone, prohibiting the use of advanced meat recovery (AMR) [derived from the skull or vertebral column] in the process of animals...." Otherwise, you are implying that AMR from the non-CNS areas presents a risk.

Similar text has been inserted.

Office of Public Health Science

Microbiology Division:

It seems HCRA should have elaborated further other than saying that they have not evaluated important source of infectivity that can reach cattle particularly dead stock and risks associated with the disposal of SRMs. These are issues of critical importance with potentially major impact on the overall BSE control programs. It is important to discuss the likely constraints such as possible lack of data that might have been the reason for not able to carry through these evaluations.

We now assume that SRMs are removed from dead stock, as well as from animals sent to slaughter.

Zoonotic Diseases & Residue Surveillance Division:

There have been several changes in the assumptions of the base case model. One of these changes appears to predict the accuracy of antemortem diagnosis of BSE by veterinarians. It is difficult from the current report and appendices to discern exactly what the 'probTestClinical' variable is representing; however, it seems to represent the probability of an antemortem inspector correctly classifying an animal as a BSE case based on its clinical signs (Appendix 1). But from the discussion in the main body of the report, it appears that the probability of showing recognizable 'clinical signs' of BSE is being conflated with the probability of a positive reaction result from BSE testing of the animal's brain tissue. These are two very different parameters and should be treated as such. In Sect 2.2.1 of the report, the designers felt it necessary to compute a probability of an animal's ambulatory status conditional on its also showing clinical signs of BSE (and it is not clear why this would be an important variable for a disease that is nearly impossible to diagnose from clinical signs alone). However, to compute that probability, numbers from the EU surveillance results of 2002 and 2003 were cited as probabilities of showing 'signs' conditional on either ambulatory or nonambulatory status. In fact, the parameter values of 3.0×10^{-5} and 5.1×10^{-4} are evidently taken from the two-year average probability of having a positive brain test for infectious BSE prions, conditional on being nonambulatory (fallen stock) or ambulatory (healthy slaughtered), respectively, at the time of testing; these values were reported in Tables 12 and 14 of the EU report cited by Harvard[1].

The authors appear to be under a very optimistic impression of the ease of clinical diagnosis of BSE for animals showing 'clinical signs' of BSE. Even if this were a country where inspectors have extensive experience in diagnosing BSE, a diagnosis rate of .95 and .85 for ambulatory and non-ambulatory animals that showing 'clinical' signs seems not at all credible. From what I have read, even for experienced clinicians in the UK, this is a disease that is extremely difficult to differentiate clinically from a host of other neurological disorders[2].

First, in response to comment (2) from Reviewer #2, we no longer rely on the European data to estimate the probability that an animal will be ambulatory as a function of clinical status. Second, both reviewer #2 and reviewer #1 also

questioned our assumption regarding the probability that a clinical animal would be detected at *antemortem* inspection. Reviewer #1 suggested that (like the present reviewer), our assumptions were too optimistic. However, Reviewer #2 suggested our assumptions were too pessimistic. In any case, Sensitivity analysis #5 suggests that the model predictions are not sensitive to this assumption.

The sensitivity analysis that invoked a doubling of the length of the incubation period was a puzzling exercise. There is no evidence in the UK that the incubation period has lengthened at all—much less, doubled—for BSE cases born after the total feed ban came into effect (BARB cases), i.e., after the level of contamination in the feed dropped to extremely low levels. Although the incidence of cases has indeed dropped very dramatically in cohorts born after the total feed ban of July 1996 (only 100 cases have been born in the UK since 31 July 1996, the onset of total feed ban), the average age at onset for those cases born through May 2005 is 5.4 years, very similar to the age at onset of cohorts born prior to 1996[3]. This would put the average incubation period at or below 5 years even for these animals exposed to extremely low levels of contaminated feed (very much the same as that calculated for animals in the earlier years of the UK epizootic). Although under experimental conditions, TSEs demonstrate an inverse dose-response relationship for length of incubation period, according to observations in the UK up to this point, there does not appear to be a relationship been exposure level and incubation period for the range of exposures experienced by cattle living under normal field conditions.

The sensitivity analysis was conducted to see what kind of impact use of an exposure-dependent incubation period might have on the results. The only data we introduce suggesting that incubation period depends on dose is the Danny Mathews personal communication. Those data do suggest a change in incubation period, even at low doses.

We agree that the quantitative estimates inferred from the data we used are at the very least uncertain. Section 3.3 of our report explains that there are other factors making it difficult to model the impact of dose-dependent incubation periods. For that reason, we did not do so and instead developed Sensitivity analysis #6 to determine what the potential impact of such an assumption might be. However, this analysis is presented as exploratory in nature.

Reference List

1. European Commission Health and Consumer Protection Directorate-General. *Report on the monitoring and testing of ruminants for the presence transmissible spongiform encephalopathiy (TSE) in the EU in 2003, including the results of the survey of prion protein genotypes in sheep breeds* [report online]. Brussels: 2004. Report No.: 04-D-420525.

2. Konold T, Bone G, Ryder S, et al. Clinical findings in 78 suspected cases of bovine spongiform encephalopathy in Great Britain. *Vet Rec*. 2004;155(21):659-66. 15581140.

3. Department for Environment Food and Rural Affairs (UK). *The Hill Report: Review of the Evidence of the Occurrence of 'BARB' BSE Cases in Cattle*

[report online]. 5 Jul 2005. Available at: http://www.defra.gov.uk/animalh/bse/pdf/hillreport.pdf. Accessed 16 Sep 2005.

U.S. Food and Drug Administration

In general, it appears that the contract obligations were met. I still have suggestions that originated with the first model concerning (e.g.) exploration of the reasons for instability that are not related to the small probabilities and simple MC sampling for extreme values.

For example, errors in conversion of text streams to numeric format can accumulate and become noticeable. Reading the input files for each iteration can accumulate errors.

> There is no evidence that text files are not read in in exactly the same way every time the simulation executes. If errors were introduced during the reading in of the files, the simulation's input file format requirements would cause the program to exit with an error message. Such an exit has not occurred even after running the program several million times.

Also, expecting desktop PCs to be stable for a week or month might be problematic.

> This issue has not been problematic to us. We have run multiple machines for several weeks at a time without experiencing a crash. The program that is running takes up very little memory and the fact that it does not cause crashes even after hundreds of thousands of successive executions indicates that it does not contain a memory leak or some other characteristic that might destabilize the operating system.

These "flaws" are not fatal; I only mention them as potential sources of sampling error in this extreme value problem.