Harvard Model of Bovine Spongiform Encephalopathy
Implications of Importing Cattle Over 30 Months of Age from Canada

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Executive Summary

The analysis described here has been conducted for USDA-APHIS, as a component of a risk assessment conducted to evaluate the impact of allowing additional cattle imports from BSE minimal-risk regions. Specifically, this analysis supports the exposure assessment component of the risk assessment and contributes to the environmental assessment.

In January 2005, USDA-APHIS published a final rule allowing some cattle imports from countries falling into a new category, designated "minimal risk regions". The rule places Canada into the minimal risk regions category and allows that country to export cattle to the U.S., so long as the animals are slaughtered prior to the age of 30 months. In order to investigate the impact of allowing the import of older cattle from Canada into the U.S. and eliminating the requirement that they be slaughtered by a specified age, APHIS conducted a risk assessment. The risk assessment estimates the likelihood that BSE-infected cattle will be imported into the U.S. given the mitigations proposed (the release assessment), the extent to which disease might spread among U.S. cattle as a result (the exposure assessment), and characterizes the resulting impacts (consequence assessment). This document supports the environmental assessment and the exposure assessment component of the risk assessment.

The analysis uses a computer simulation model developed for USDA by the Harvard Center for Risk Analysis[1]. A series of modifications to the model have been implemented. The most important modifications for the purpose of this analysis include enhanced capabilities for specifying the import of infected cattle; and explicit modeling of cattle exposure to the BSE agent via administration of poultry litter in cattle feed. For the purpose of completeness, this report documents all modifications to the function of the model and to its assumptions made since the release of initial Harvard BSE risk assessment (1).

In order to characterize the impact of uncertainty, the analysis evaluates the impact of using pessimistic assumptions for the rate of mislabeling and contamination, the rate of on-farm misfeeding of prohibited feed to cattle, the prevalence of various rendering technologies used in

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[1] While on the research staff at the Harvard Center for Risk Analysis, the author of this report was a lead developer of the Harvard BSE simulation model. He has been involved in several risk assessments conducted using that software. Dr. Cohen moved to the Tufts New England Medical Center in January, 2006.

the U.S., the proportion of poultry litter that is used in cattle feed, and the prevalence of BSE in Canada.

Under base case conditions, the results of this analysis indicate that the expected number of infected cattle in the U.S. over 20 years as a result of importing cattle from Canada would amount to 21 animals. Most of these infected animals (approximately 90%) would be imported directly, while the remaining 10% would represent secondary infections (*i.e.*, native U.S. cases). Potential human exposure over this 20-year period would be expected to amount to 45 cattle oral ID_{50}s. Of the five uncertain parameters considered in the sensitivity analyses, the model is most sensitive to the release of infectivity (as expressed by BSE prevalence in Canada). Simultaneous assignment of pessimistic values to all five of the uncertain assumptions considered here increases the predicted number of secondary BSE cases to 42 on average, with total potential human exposure increasing to 290 cattle oral ID_{50}s over 20 years. Under all cases, the reproductive constant for BSE (R_0) remains less than 1 with high probability, indicating exponential growth in the number of native U.S. cases following potential introduction from Canada is unlikely. Equivalently, the results indicate that in the absence of a continual introduction of BSE into the U.S., its prevalence will decrease over time, eventually leading to its elimination. It is important to note that this set of findings reflects the simultaneous use of pessimistic values for a range of assumptions, including the assumptions identified as being influential in earlier analyses (1), as well as the assumed prevalence of BSE in Canada.

1 Introduction

The analysis described here has been conducted for the USDA Animal and Plant Health Inspection Service (APHIS) as part of a risk assessment conducted to evaluate the impact of allowing additional cattle imports from BSE minimal-risk regions. Specifically, this analysis supports the exposure assessment component of the risk assessment and contributes to the environmental assessment.

In response to Canada's May 2003 discovery of a dairy cow in Alberta province infected with bovine spongiform encephalopathy (BSE), the U.S. Department of Agriculture (USDA) banned the import of cattle from that country. The border closure reflected U.S. policy that prohibited such imports from countries with indigenous cases of BSE. Since that initial discovery, eight additional BSE-infected cattle from Canada have been discovered, one of which had been exported to the U.S.

In January 2005, USDA-APHIS published a final rule allowing some cattle imports from countries falling into a new category, designated "minimal risk regions". The rule places Canada into the minimal risk regions category and allows that country to export cattle to the U.S., so long as the animals are slaughtered prior to the age of 30 months. In order to investigate the impact of allowing the import of older cattle from Canada into the U.S. and eliminating the requirement that they be slaughtered by a specified age, APHIS conducted a risk assessment. The risk assessment estimates the likelihood that BSE-infected cattle will be imported into the U.S. given the mitigations proposed (the release assessment), the extent to which disease might spread among U.S. cattle as a result (the exposure assessment), and characterizes the resulting impacts (consequence assessment). This document supports the environmental assessment and the exposure assessment component of the risk assessment.

The analysis described here uses the BSE simulation developed by the Harvard Center for Risk Analysis (HCRA) (1;2). Using this model, the analysis estimates the extent to which the introduction of BSE from Canada will contribute to the prevalence of BSE among cattle in the U.S. In addition to describing the contribution to prevalence, the model also describes the ability of safeguards in the U.S. to eliminate BSE in terms of the disease's reproductive constant, designated R_0. The R_0 parameter is the average number of new BSE cases resulting from each existing BSE case. A value of R_0 greater than 1.0 indicates that prevalence increases over time

(because each existing case gives rise to more than one new case on average), while a value of R_0 less than 1.0 indicates that prevalence decreases over time. The HCRA BSE model reports other information, including the potential for human exposure to the BSE agent.

Strictly speaking, an analysis of the impact of eliminating age restrictions on cattle imports from Canada would compare the proposed regulation to the status quo, which, as noted above, allows the import of cattle from Canada, so long as they are slaughtered prior to the age of 30 months. This analysis develops a more conservative "bounding" estimate of the incremental impact of eliminating age restrictions on animal health and human exposure because it does not "subtract" risks associated with status quo policies.

In addition to the base case scenario, this analysis presents sensitivity analyses to evaluate the impact of alternative plausible assumptions identified in earlier work (1;2) as having the most important impact on the simulation results. In addition to evaluating the impact of these assumptions, this assessment also investigates the impact of assigning pessimistic values to the proportion of poultry litter used in cattle feed, and to the prevalence of BSE in Canada.

The remainder of this paper has two sections. Section 2 describes the methodology, including parameter assumptions and revisions to the Harvard simulation model for this project. Section 3 details results and discusses the findings.

2   Methods

The BSE simulation model used in this analysis was first described by Cohen *et al.* (1;2). The functionality of that model has since been modified to accommodate the requirements of an analysis conducted for the USDA Food Safety Inspection Service (FSIS) to evaluate regulatory changes that influence the risk pathway. Section 2.1 describes the modifications, as well as additional modifications that have been made for this analysis. The base case scenario builds on the base case analysis described by Cohen *et al.* (1) and subsequently revised for FSIS in Cohen and Gray (3). Section 2.2 describes the base case scenario for this analysis representing conditions in the U.S. if imports of older cattle from Canada are allowed. Finally, Section 2.3 describes sensitivity analyses conducted for the purpose of characterizing the extent to which the findings of this analysis depend on assumptions made for critical parameters.

Note that the analysis conducted for FSIS represents a "layer" of simulation and parameter revisions made on top of the original BSE model described by Cohen *et al.* in October 2003 (1). The analysis described here therefore represents a second layer of simulation and parameter revisions. In order to save the reader the trouble of having to refer back to both of the previous documents and sequentially reconstructing the series of changes described, this document effectively subsumes the relevant changes to the FSIS report (3) and incorporates text from that report as needed to describe the changes that were made as part of that effort. Where appropriate, this document indicates where material has been taken verbatim or with some modifications from that report.

Finally, note that, as described in the introduction to the methodology section in the FSIS report, this analysis uses central estimates for the base case assumptions where possible. However, in the few limited cases where doing so is not feasible, this analysis attempts to err on the side of using assumptions that overstate the extent to which BSE might spread in the U.S. (*i.e.*, so-called "conservative" assumptions). To the extent that the findings here show that introduction of BSE into the U.S. does not pose a substantial risk, the use of these conservative assumptions does not compromise the qualitative implications of this report's findings. In any case, use of conservative values was largely limited to parameters that, based on earlier work (1), are known not to have a substantial impact on the simulation results.

2.1   Revisions to the Harvard Simulation Model

Eight sets of changes to the Harvard simulation model have been implemented for the purpose of this and other analyses conducted since the release of the assessment conducted by Cohen *et al.* (1). This section describes those changes. These include changes made for FSIS (3): addition of ambulatory status as a characteristic that factors into *antemortem* inspection findings (Section 2.1.1); changes to the operation of the *antemortem* inspection process (Section 2.1.2); addition of tonsils as a tissue category (Section 2.1.3); changes to SRM inspection (Section 2.1.4); addition of supplemental reports that detail contamination of human food by animal age and ambulatory status (not used in this report) (Section 2.1.5); and changes made specifically for APHIS in this analysis: enhanced capabilities for specifying the import of infected cattle over the course of the simulated period (Section 2.1.6); separate specification of SRM inspector, rendering, and disposition of rendered material (MBM transport) for healthy slaughter and dead animals (Section 2.1.7); and explicit modeling of cattle exposure to the BSE agent via

administration of poultry litter in cattle feed (Section 2.1.8). Sections 2.1.1 through 2.1.5 are taken directly from Cohen and Gray (3), and the remaining three sections are new.

It should be emphasized that not all of these capabilities are used in all analyses, and in particular, this analysis uses only a subset of the capabilities described here. Section 2.2 describes the specific assumptions made for this analysis.

2.1.1   Ambulatory Status (From Cohen and Gray (3))

USDA now prohibits the use of non-ambulatory animals for human food. In order to represent this policy in the simulation model, along with others that may place restrictions on the use of these animals in feed, the simulation has been modified so that it tracks the ambulatory status of cattle infected with BSE. The simulation can designate an animal as non-ambulatory when the animal becomes infected with BSE or when the animal develops clinical signs of BSE. Once an animal becomes non-ambulatory, it cannot become ambulatory at a later time during the simulation. This framework is consistent with non-ambulatory status being assigned to an animal at *antemortem* inspection. Appendix 1 details the assignment of parameter values to control this feature.

2.1.2   Operation of the *Antemortem* Inspector (From Cohen and Gray (3))

Tasks performed by the *antemortem* inspector are now divided into two steps. As part of the first step, inspection, the *antemortem* inspector determines 1) whether the animal passes inspection based on considerations not related to BSE, and 2) whether the animal shows clinical signs of BSE. As part of the second step, allowed use designation, the *antemortem* inspector designates the animal as allowed for use in human food, animal feed, or both feed and food based on the two determinations made in the inspection step, and on the animal's ambulatory status.

Inspection: The *antemortem* inspector makes two judgments. First, it determines if the animal passes or fails inspection based on considerations not related specifically to the manifestation of clinical BSE signs. The probability that an animal will pass inspection based on non-BSE considerations depends on 1) its ambulatory status, and 2) its age. The second determination made by the *antemortem* inspector is whether the animal displays clinical signs of BSE. This finding depends on the animal's ambulatory status and on whether the animal is, in

fact, clinical. Note that it is possible for the inspector to fail to identify a clinical animal as displaying BSE signs. That is, this feature makes false negative findings possible.

Allowed use designation: The *antemortem* inspector follows two sets of deterministic rules, one of which governs whether an animal can be used in human food, and the other which governs when an animal can be used in animal feed. In both cases, the designation depends on three factors: 1) whether the animal passed inspection for non-BSE related factors, 2) whether the *antemortem* inspector identified the animal as displaying clinical signs of BSE, and 3) whether the animal is non-ambulatory.

Appendix 1 details the assignment of parameter values to control the behavior of the *antemortem* inspector. As configured for the analyses described in this report, the *antemortem* inspector prohibits use of cattle tissue in feed only if the animal displays clinical signs of BSE. Although in reality, there is no such explicit requirement governing *antemortem* inspection, this characterization of the *antemortem* inspector's operation makes sense within the context of the simulation model. In particular, the simulation explicitly models only animals that have been infected with BSE. Moreover, the base case assumes that only animals that have reached the clinical stage of disease display clinical signs consistent with BSE. In the "real world," such animals would be most likely tested for the BSE agent after slaughter and would test positive with very high probability (because they have reached the end of the incubation period and because the screening tests are geared to minimize false negative results). After testing positive, the carcasses from such animals would be destroyed. That is, as is effectively assumed in the simulation, the tissue from such animals could not be used in either human food or in animal feed.

2.1.3 Tonsils (From Cohen and Gray (3))

Tonsils have been added as a tissue category.

2.1.4 SRM Inspection (From Cohen and Gray (3))

The original BSE simulation model (1) eliminated infectivity using the SRM inspector only when animals were sent to slaughter. That is, the SRM ban did not apply to dead stock. The model has been revised so that it can remove infectivity from dead stock, as well.

2.1.5 Supplemental Reports (From Cohen and Gray (3))

The simulation model can now report distributions for the number of cattle oral ID_{50}s in human food (by tissue) for cattle by age range and ambulatory status. As now configured, the simulation can create separate reports for each combination of the following age ranges (0 to 11 months, 0 to 23 months, 0 to 29 months, 30+ months, and all ages) and ambulatory status designations (normal, non-ambulatory).

2.1.6 Import of Infected Cattle

The original model allowed the import of infected cattle only once, at the beginning of the simulation. The model now allows for the periodic import of infected cattle. The model allows the specification of the animal type (dairy, beef slaughter, or reproductive beef), gender, age at import, the import rate for infected animals (i.e., the Poisson distribution parameter), the age at infection, and optionally, a scheduled slaughter age. This last parameter can be used to specify that animals must be slaughtered within a fixed amount of time after import. Alternatively, if no specific slaughter age is specified, the simulation assimilates the animals into the U.S. cattle population and slaughters them at random using the appropriate probabilities specified for native U.S. cattle.

2.1.7 Separate Slaughter and MBM Production for Dead and Healthy Slaughter Cattle

The revised simulation model now allows for the specification of distinct parameter values governing SRM inspection, rendering, and disposition of processed proteins for dead and healthy slaughter cattle. The revision was made to allow for the possibility that the segment of the rendering industry that processes dead animals is distinct from the segment of the industry that processes healthy slaughter animals. In addition, it is possible that the effectiveness of SRM removal for healthy slaughter animals will differ from the corresponding effectiveness for dead cattle.

Because the model allows distinct specification of rendering, SRM inspection and processed tissue disposition for dead and healthy slaughter cattle, a feature has been added that allows non-ambulatory cattle to be treated like either dead cattle or like healthy slaughter animals. If the user chooses to treat non-ambulatory cattle like dead cattle, tissue from these animals will not be available for human consumption. In addition, 1) the SRM inspector, renderer, and MBM

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transport parameters for dead animals will govern processing of non-ambulatory animals; 2) non-ambulatory cattle will be disposed of on the farm with the same probability as animals that die on the farm; and 3) the use of such cattle in animal feed is subject to restrictions imposed by *antemortem* inspection. If the user chooses to treat non-ambulatory animals like healthy slaughter animals, then the tissue from these animals can be used in human food (as well as in animal feed), depending on assumptions specified for the *antemortem* inspection[2]. In addition, the SRM inspector, renderer, and MBM transport parameters for healthy slaughter animals will govern processing of non-ambulatory animals.

Finally, if the user chooses to treat non-ambulatory cattle like healthy slaughter animals, tissue from these animals may be available for use in human food, subject to constraints imposed by *antemortem* inspection.

2.1.8   Explicit Modeling of Recycling of Cattle Tissue in Poultry Feed

The simulation model allows the user to specify the proportion of the MBM produced that is used in poultry feed (separate values can be specified for dead and healthy slaughter cattle), and the proportion of poultry litter that is administered to cattle. The model assumes that 100% of infectivity in poultry feed ends up in poultry litter. As a result, the proportion of MBM infectivity that ends up in cattle feed via this pathway is the product of the proportion of MBM sent to poultry feed producers, and the proportion of poultry litter that is used in cattle feed.

2.2   Base Case Assumptions

This section outlines changes made to the base case assumptions used in the earlier risk assessment (1) and implemented in the current analysis. Revisions discussed include those related to the assignment of ambulatory status (Section 2.2.1), those related to *antemortem* inspection (Section 2.2.2), assumptions regarding the amount of infectivity in tonsils (Section 2.2.3), assumptions related to the level of compliance with the feed ban (Section 2.2.4), new assumptions regarding the use of animals for the generation of T-bone steaks and other uses of bone-in-beef (Section 2.2.5), new assumptions regarding the disposition of dead animals (Section 2.2.6), new assumptions regarding the disposition of rendered products (Section 2.2.7), modifications to the assumed proportion of various tissues made available for human

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[2] For this analysis, tissue from non-ambulatory animals cannot be used in human food.

consumption (Section 2.2.8), and new assumptions regarding misfeeding (Section 2.2.9). Section 2.2.10 describes the assumed introduction of infected cattle into the U.S. in the base case scenario.

2.2.1   Assignment of Ambulatory Status (From Cohen and Gray (3) with Modifications)

The revised model now requires specification of ambulatory status probability conditional on whether an animal displays clinical signs of disease. For animals that show no signs, this analysis assumes that the probability of being non-ambulatory, designated $P(NA \mid NS)$, is the same as the unconditional probability of being non-ambulatory, designated *P(NA)*. This latter probability is simply the proportion of cattle in the entire population that are non-ambulatory.

Although data are not currently available, this analysis assumes approximately 1 in 200 animals is nonambulatory. That is, it is assumed that P(NA) is 0.5% and hence that $P(NA \mid NS)$ is 0.5%. As shown in Cohen and Gray (3), this assumption has only a limited impact on the simulation results.

The probability that animals with clinical BSE signs are non-ambulatory, designated $P(NA \mid S)$, can be calculated using Bayes formula. In particular

$$P(NA \mid S) = \frac{P(S \mid NA)P(NA)}{P(S \mid NA)P(NA) + P(S \mid A)P(A)}, \tag{1}$$

where $P(S \mid NA)$ is the probability that an animal displays clinical BSE signs given that it is non-ambulatory, and $P(S \mid A)$ is the probability it displays clinical signs given that it is ambulatory. The most extensive BSE compliance data have been collected in Europe (4). However, the European surveillance data do not document ambulatory status. Cohen and Gray (3) investigated a range of values for $P(NA \mid S)$ ranging from 8% (base case) to as high as 100% (see Sensitivity Analysis 8 in that report). Their analysis showed that the value assigned to this parameter had only a minor impact on the simulation results.

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2.2.2 *Antemortem* Inspection (From Cohen and Gray (3) with Modifications)

Probability of passing inspection for non-BSE factors – For animals with normal ambulatory status, this analysis uses the pass probabilities used by Cohen *et al.* (1). It is assumed here that non-ambulatory animals do not pass *antemortem* inspection. Note that Cohen *et al.* (1) showed that the simulation results are not sensitive to assumptions about the performance of the *antemortem* inspector. In addition, as described below, this analysis assumes that material derived from non-ambulatory animals cannot be used in human food. On the other hand, non-ambulatory status does not affect use of tissue in animal feed.

Probability that antemortem inspector will discover a clinical animal – Cohen *et al.* (1) assumed that the *antemortem* inspector passes (i.e., fails to successfully identify) 10% of all animals with clinical signs of BSE. That is, that report assumed *antemortem inspection* identifies clinical animals with 90% probability. This analysis assumes that it is more difficult for inspectors to identify non-ambulatory animals as having BSE because there is no opportunity to observe their movements. As a result, it is assumed here that the *antemortem* inspector identifies clinical animals as showing BSE signs with 95% probability if the animal is ambulatory, and with 85% probability if the animal is non-ambulatory. That is, non-ambulatory animals with clinical signs are more difficult to discover than clinical animals that are still ambulatory.

Antemortem rules for use of animals in human food – In the base case, an animal can be used in human food so long as it is ambulatory and passes both aspects of the *antemortem* inspection – *i.e.*, 1) the animal must pass the inspection for non-BSE factors, and 2) the inspector does not identify the animal as showing clinical BSE signs.

Antemortem rules for use of animals in animal feed – In the base case, an animal can be used to produce animal feed so long as the inspector does not identify the animal as showing clinical BSE signs.

Disposition of Nonambulatory Animals – As noted in Section 2.1.7, the simulation allows the user to specify that non-ambulatory animals be treated like animals that die prior to being sent to slaughter. In this case, the animals are disposed of "on the farm" with the same probability as dead animals. When disposed of on the farm the BSE agent in the carcass cannot contaminate either animal feed or human food. When non-ambulatory animals are not disposed of on the

farm, this option causes them to be processed in the same way that dead animals are processed when they are not disposed of on the farm (SRM removal rates, rendering reduction technologies, and disposition assumptions for rendered product). However, this analysis assumes that non-ambulatory animals are treated like healthy slaughter animals, although the disposition of the resulting materials is subject to limitations imposed by *antemortem* inspection rules.

2.2.3   Infectivity in Tonsils (From Cohen and Gray (3))

Recent information suggests that bovine tonsils may carry BSE infectivity (5). A pathogenesis study found that inoculating the brains of calves with tonsil tissue from BSE-infected cattle successfully transferred the disease. Specifically, one out of five calves inoculated intra-cerebrally (*i.c.*) with tonsil from animals 10 months post infection developed BSE. No other time points (6, 18, or 21 months post infection) have resulted in inoculated calves developing BSE (5;6).

The Scientific Panel on Biological Hazards of the European Food Safety Authority estimated from the results of the pathogenesis study that a 50 gram tonsil would contain no more than 0.005 bovine oral ID_{50}s. An analysis by Det Norske Veritas (DNV), using a different assumption for the differential effectiveness of *i.c. vs.* oral exposure, estimated the infectivity in a 50 gram tonsil to be approximately 0.25 bovine oral ID_{50}s (cited in (5)). The corresponding total in a pair of tonsils is 0.5 bovine oral ID_{50}s.

Assuming an incubation period of 36 months, which has been typical in the pathogenesis study, this analysis estimates 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.* (1)). Hence, the total infectivity in tonsils implied by the DNV calculations amounts to 0.2% of the total infectivity in the entire animal (0.5 ÷ 250 oral ID_{50}s). This analysis assumes that the tonsils maintain this same fraction of infectivity throughout the BSE incubation period. Given the extremely small proportion of infectivity estimated to be present in tonsils, this simplifying assumption can have at most a negligible impact on the simulation results. In order to maintain the same total quantity of infectivity in an animal assumed by Cohen *et al.* (1), this analysis multiplies the tissue-specific fractions for other tissues at each age point by 99.8%.

2.2.4   Feed Ban Compliance Rates (From Cohen and Gray (3) With Modifications)

This analysis uses government surveillance data to estimate probabilities for mislabeling and contamination in MBM and feed production facilities. Mislabeling occurs when a renderer or feed manufacturer incorrectly labels prohibited product as non-prohibited. Contamination occurs when MBM or feed not labeled as containing a prohibited product is tainted with prohibited product. Contamination can occur in mixed facilities (facilities that manufacture product containing prohibited material and product designated as not containing prohibited material on the same production line) and is presumably made worse by incomplete cleanout procedures when production is switched from prohibited to non-prohibited product.

Since the publication of Harvard's November, 2001 BSE risk assessment (7), additional information on compliance with the 1997 feed rule has become available. The U.S. FDA Center for Veterinary Medicine (CVM) has collected and disseminated the state and FDA inspection results for facilities that handle prohibited material (*i.e.*, ruminant derived protein, with some exceptions). This information (see http://www.accessdata3.fda.gov/BSEInspect) quantifies the number of facilities out of compliance with the feed rule and hence serves as a useful starting point for this report's analysis. However, because the U.S. FDA databases do not report the size of these facilities (*i.e.*, total material throughput), an assumption must be made regarding the size of the non-compliant facilities compared to other facilities. For this purpose, this analysis assumes that the non-compliant facilities are the same size on average as facilities not cited for feed rule violations. This assumption is likely to be conservative because inspectors report that smaller firms are more likely to be cited for violations of various sorts than larger ones (personal communication, Neal Bataller, FDA/CVM, May, 2004).

In order to estimate mislabeling and contamination probabilities, this analysis relies on data collected by FDA/CVM[3] prior to September 2003. FDA/CVM data collected prior to September 2003 better detail the nature of the violations discovered, reporting the total number of firms with at least one violation and designating each violation as a case in which: 1) products were not labeled as required, 2) the facility did not have adequate systems to prevent co-mingling, or 3) the facility did not adequately follow record keeping regulations. More recent data report

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[3] Compliance program implementation details can be found at
http://www.fda.gov/cvm/CVM_Updates/BSE0305.htm .

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violations only in terms of the type of action indicated – *i.e.*, Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI). FDA (8) defines these terms[4].

Table 1 reproduces the April 2002 FDA Update (9), the most recent summary reported prior to the September, 2003 change in database and reporting details. The data summarized here are limited to facilities handling prohibited materials.

Table 1
April, 2002 Results of Inspections at Facilities Handling Prohibited Materials

Facility Type	Inspected (N)	Cited for Mislabeling (N)	Cited for Mislabeling Percent	Cited for Commingling (N)	Cited for Commingling Percent
Renderers	171	4	**2.3%**	3	**1.8%**
Feed mills					
Licensed Feed Mills	370	8	2.2%	2	0.5%
NL Feed Mills	1224	55	4.5%	28	2.3%
Total	1594	63	**4.0%**	30	**1.9%**
Other Firms[(a)]	2153	77	3.6%	34	1.6%

Notes:

   (a)   Other firms include ruminant feeders, on-farm mixers, protein blenders, and distributors

Use of data collected prior to the December 23, 2003 discovery of a BSE case in Washington state is likely to produce conservative compliance estimates because compliance rates have most likely improved in the wake of that discovery. For example, June, 2005 FDA

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[4] According to FDA, "An OAI inspection classification occurs when significant objectionable conditions or practices were found and regulatory sanctions are warranted in order to address the establishment's lack of compliance with the regulation. An example of an OAI inspection classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented" (8).

"A VAI inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the Ruminant Feed Ban. These include provisions such as minor recordkeeping lapses and conditions involving non-ruminant feeds" (8).

compliance data (10) indicate that only 1.1% of rendering firms (2 of 176) were cited for any OIA violation. For feed mills, the corresponding figure was 0.1% (3 of 2,331).

The parameters adopted for this report's analysis are shaded in Table 1 and reproduced in Table 2 for the purpose of comparing them with assumptions made in the earlier risk assessment (1).

Table 2
Assumptions for Mislabeling and Contamination

| Parameter | MBM Production | | | | Feed Production | | | |
| | 2003[a] | | This Analysis | | 2003[a] | | This Analysis | |
	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case	Base Case	Pess-imistic Case
Probability of Contamination	14%	25%	1.8%	14%	16%	16%	1.9%	16%
Proportion of Prohibited Material Transferred to Non-Prohibited Material per Contamination Event	0.1%	1%	0.1%	0.1%	0.1%	1%	0.1%	0.1%
Mislabeling Probability	5%	10%	2.3%	5%	5%	33%	4%	5%

Notes:
   (a)   Values from Cohen et al. (1).

Although the base case parameter values reflect several conservative assumptions, Cohen and Gray (3) showed that even substantial modifications to these rates have at most a modest impact on the simulation results (see Sensitivity Analysis #1 in that report). It is therefore likely that any conservative impact resulting from these assumptions would likewise be modest.

2.2.5   Consumption Rates for Bone-in-Beef (From Cohen and Gray (3))

Cohen *et al.* (1) assumed that slaughter facilities do not produce bone-in cuts of beef from animals over 24 months of age[5]. These cuts are potentially important because they may contain spinal cord, dorsal root ganglia (DRG) or both. At the request of USDA-FSIS (3), and based on

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[5] Discussed in Cohen et al. (1) Appendix 1 at 2.18.3

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the judgment of USDA-FSIS personnel, this analysis has revised these assumptions to reflect use of bone-in cuts of beef from animals 24 months of age and over. In particular, this analysis assumes that for all animals 12 months of age and older, 30% of spinal cord ends up in bone-in-beef (category "bone") when the spinal cord is not removed during processing. This analysis also assumes that for all animals, 30% of DRG is available for potential human exposure as a result of consuming bone-in-beef (category "bone"). These uses may include specific cuts of beef like T-bone steaks and other uses of these bones, including soup and stock production. The use of spinal cord of cattle 30 months of age and older is banned from human consumption (Federal Register / Vol. 69, No. 7 / Monday, January 12, 2004 / Rules and Regulations).

2.2.6 Disposition of Dead Animals

Table 3 details recent estimates of the proportion of animals that are rendered among downers and those that die prior to slaughter.

Table 3
Proportion of Animals Rendered Among Downers and Those That Die Prior to Slaughter

Category	Total Mortality and Downers	Proportion Rendered
Informa Economics (11)		
Older cattle		
Dairy	584,550	62%
Feedlot	300,000	94.4%
Beef cows	1,025,750	20.7%
Total	1,910,300	44.7%
Calves	2,365,600	27.4%
Calves and older cattle	4,275,900	35.1%
U.S. FDA (12), Table 2		
All dead cattle under 500 pounds	2,365,000	5%
Dead cattle from feedlots	300,000	90%
Beef cows	1,400,000	10%
Dairy cows	400,000	60%
Total	4,465,000	17%

In response to comments on its initial analysis and the differences between FDA and Informa estimates, FDA substituted new industry data into the analysis and revised its estimate from 17 percent to 33 percent with an upper bound of 42%. FDA acknowledges uncertainty in the estimates. This analysis adopts U.S. FDA's estimate that 42% of cattle that die prior to

slaughter are rendered (p. 58,588 in (13)). This value is considered by FDA to be an upper bound for this parameter.

2.2.7   Disposition of Rendered Materials

The 2003 risk assessment (1) assumed that approximately 30% of prohibited MBM and non-prohibited MBM is either exported or used in pet food and hence is not available to contaminate domestic cattle feed. While 15% to 30% of MBM produced in the U.S. has typically been exported, that proportion dropped substantially in 2004, to 5% of production. Demand abroad for poultry by-product from the U.S. has remained relatively strong. This analysis therefore assumes that 95% of domestically produced prohibited MBM remains in the U.S. and is available for use in animal feed. For non-prohibited product, this analysis assumes that 70% remains in the U.S. and is available for use in animal feed. Table 4 details the assumed disposition of MBM by type of renderer and type of product.

Table 4
Disposition of MBM

| | Type of Renderer and Type of MBM | | | | | |
| | Prohibited Ingredient Renderer | | Non-Prohibited Ingredient Renderer | | Mixed Type Ingredient Renderer | |
	P	NP[b]	P	NP	P	NP
P Feed Producer (excluding poultry feed)	50%	50%	NA[a]	50%	50%	50%
NP Feed Producer	0%	10%	NA[a]	10%	0%	10%
Mixed Feed Producer	5%	10%	NA[a]	10%	5%	10%
Poultry Feed Producer	40%	0%	NA[a]	0%	40%	0%
Out (Unavailable to U.S. Cattle)	5%	30%	NA[a]	30%	5%	30%

Abbreviations: P – prohibited, NP – non-prohibited

Notes: (a)   This analysis assumes no product from a non-prohibited renderer is labeled as prohibited

(b)   Prohibited ingredient renderers may produce feed that is mislabeled as non-prohibited.

Finally, of the infectivity that ends up in poultry feed and ultimately in poultry litter (see Section 2.1.8), this analysis assumes that 1% is used in cattle feed, close to an estimate reported by American Proteins, Inc. (personal communication from Kevin Custer, Vice President of American Proteins, to Lisa Ferguson, USDA APHIS, November 15, 2005).

2.2.8   Food Inspector

For animals 30 months of age and older, this analysis assumes that 1% of SRMs are potentially available for human consumption (brain, spinal cord, dorsal root ganglia [DRG], gut, eyes, AMR-derived meat, bone, and trigeminal ganglia [TGG]). This estimate is based on FSIS data on compliance with the regulations related to Specified Risk Materials (SRMs) (http://www.fsis.usda.gov/Fact_Sheets/BSE_Rules_Being_Strictly_Enforced/index.asp).

2.2.9   The Misfeeding Rate

Cohen *et al.* (1) assumed that 1.6% of correctly labeled prohibited feed was administered to cattle (the misfeeding rate), and that the worst case value for this parameter is 15%. More recent data (www.ngfa.org/article.asp?article_id=5460, last viewed June 5, 2005) indicate that the worst case value for this parameter is 5%, i.e., that a rate of 15% is unrealistically pessimistic.

2.2.10   Import of Infected Cattle

This section describes the assumed base case introduction of infected cattle into the U.S. as the result of importing bovine livestock from Canada.

Assumed Introduction of Infected Cattle

The release assessment quantifies the rate at which cattle are imported annually from 2007 through 2026 in each of the following categories: slaughter cattle (steers and heifers, cows, bulls and stags, and calves); stockers/feeders; and breeding cattle.

For the purpose of developing parameter input files, each of these groups must be described in terms of their type (BEEF, BEEFREPRO, or DAIRY), gender (MALE or FEMALE), age (in months), the annual rate at which infected animals in this group are imported (Poisson distribution parameter), age at infection (months), age to be slaughtered (or no age, indicating that the imported animals are to be integrated into the U.S. cattle population). Table 5 divides each of the groups defined in the release assessment into groups with each of these characteristics defined. Note that when these groups are divided across genders or into different age groups, the proportions in the two right-most columns are used to apportion the total. The

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values in Table 5 represent the assumed import rates for the base case scenario for the year 2007. For other years, the total import rate for animals in the release group is different, resulting in different estimates for the rate at which infected animals are imported. All other entries in the table are the same for other import years. Finally, note that the age groups identified represent a discrete characterization of what is in reality a more continuous set of values. For example, steers and heifers aged 17, 18, and 19 months old are imported, in addition to those aged 16 or 20 months old (groups specified in Table 5).

Table 5
Apportionment of Release Assessment Import Groups

Release Assessment Group	Type	Gender	Age (Months)	Annual Import Rate	Age at Infection (Months)	Age at Slaughter (Months)	Total Imported in Release Group	Gender Fraction	Age Fraction
SLAUGHTER									
Steers and Heifers	BEEF	MALE	16	0.01	1	16	727,802	60%	5%
	BEEF	MALE	20	0.13	1	20	727,802	60%	45%
	BEEF	MALE	24	0.13	1	24	727,802	60%	45%
	BEEF	MALE	30	0.01	1	30	727,802	60%	5%
	BEEF	FEMALE	16	0.01	1	16	727,802	40%	5%
	BEEF	FEMALE	20	0.10	1	20	727,802	40%	50%
	BEEF	FEMALE	24	0.08	1	24	727,802	40%	40%
	BEEF	FEMALE	30	0.01	1	30	727,802	40%	5%
Cows	BEEFREPRO	FEMALE	60	0.02	1	60	115,424	100%	20%
	BEEFREPRO	FEMALE	72	0.04	1	72	115,424	100%	50%
	BEEFREPRO	FEMALE	84	0.02	1	84	115,424	100%	30%
	DAIRY	FEMALE	36	0.02	1	36	173,136	100%	20%
	DAIRY	FEMALE	46	0.06	1	46	173,136	100%	50%
	DAIRY	FEMALE	72	0.04	1	72	173,136	100%	30%
Bulls and stags	BEEFREPRO	MALE	66	0.04	1	66	53,658	100%	100%
Vealers/light calves	BEEF	MALE	4	0.02	1	4	51,286	70%	100%
	BEEF	FEMALE	4	0.01	1	4	51,286	30%	100%
BREEDING									
Dairy cows/heifers	DAIRY	FEMALE	17	0.03	1	none[b]	49,560	100%	100%
Beef cows/heifers	BEEFREPRO	FEMALE	17	0.00	1	none[b]	4,909	100%	100%
Bulls	BEEFREPRO	MALE	20	0.00	1	none[b]	3,087	100%	100%
STOCKER/FEEDER									
All	BEEF	MALE	12	0.09	1	17	189,139	70%	100%
	BEEF	FEMALE	12	0.04	1	17	189,139	30%	100%

Notes

(a)   *The scaled import rate is equal to the product of 1) the annual import rate for the release group (e.g. 727,802 for steers and heifers in 2007); 2) the gender fraction; 3) the age fraction; AND 4) the BSE prevalence rate 0.68×10^{-6} in the base case, which equals the expected value for prevalence calculated using the Bayesian birth cohort method UK feed ban data).*

(b)   *These animals are integrated into the U.S. cattle population and hence have no definitive age at slaughter. Each month, they might be slaughtered, depending on the slaughter probability assigned their type, age, and gender.*

2.3 Sensitivity Analyses (From Cohen and Gray (3) with Modifications)

As in the 2003 risk assessment (1), this assessment includes a series of univariate analyses to identify potentially important assumptions. These assumptions are conducted by holding all but one set of assumptions equal to their base case values. The set of assumptions to be evaluated are set equal to pessimistic values to see if doing so influences key model predictions – in particular, for this analysis, the predicted number of cattle infected with BSE in the U.S. over a 20-year period.

The sensitivity analyses conducted here evaluate the impact of alternative assumptions for specific parameters identified as influential in the original analysis (1). This assessment also investigates other assumptions, as described below. The goal of this sensitivity analysis was to investigate the extent to which alternative plausible assumptions might increase the estimated risk associated with importing cattle from Canada.

Sensitivity analyses include:

- *Sensitivity 1* – Mislabeling and contamination – This analysis revises the base case values for these parameters to take into account new data on compliance rates. The sensitivity analyses evaluate the impact of these revisions by using the previous base case values from Harvard's October, 2003 report as the worst case values in the current analysis. In particular, it increases the mislabeling rates to 5% for both MBM and feed production. This sensitivity analysis increases contamination rates to 14% (MBM production) and 16% (feed production) (see Section 2.2.4).

- *Sensitivity 2* – Misfeeding – The base case value for this parameters is 1.6%. This analysis investigates the impact of using the pessimistic value of 5% for this parameter (see Section 2.2.9).

- *Sensitivity 3* – The render reduction factor – This analysis changes the distribution of render reduction factors using the worst case assumptions for this parameter from Harvard's October, 2003 report.

- *Sensitivity 4* – The proportion of poultry litter used in cattle feed. The base case value for this parameter is 1%. The sensitivity analysis investigates use of 5% for this parameter.

- *Sensitivity 5* – The prevalence of BSE in Canada – In place of the base case prevalence of 0.68×10^{-6} (the expected value for prevalence calculated using the Bayesian birth cohort method UK feed ban data), the sensitivity analysis uses a value of 3.9×10^{-6} (the expected value calculated using the BSurvE Prevalence B estimate without including feed ban data).

- *Sensitivity 6* – All assumptions from Sensitivity Analyses 1, 2, 3, 4, and 5. In this analysis, all 5 parameters analyzed in the preceding sensitivity analyses are set to their pessimistic values.

3   Results and Discussion (Introduction From Cohen and Gray (3) with Modifications)

Detailed results of this report's analysis appear in Appendix 2. Appendix 2A summarizes the overall results from each simulation, including epidemic statistics (number of animals infected, *etc*.), frequency of different modes of infection, frequency for different modes of death (natural death *vs.* slaughter), the flow of infectivity through the rendering and feed production system, and potential human exposure to the BSE agent (cattle oral ID_{50}s) by tissue type. Appendix 2B contains a series of 12 graphs for each simulation scenario.

The graphs and tables in Appendix 2 summarize distributions for each of the model's output values. Note that the distributions for each scenario arise as the result of modeled stochastic phenomena corresponding to that scenario's assumptions. For example, the base case scenario assumes that 5% of the rendering facilities do not reduce infectivity levels (*i.e.*, they have a render reduction factor of 1.0). However, the proportion of BSE-infected animals actually sent to such facilities varies from simulation trial to simulation trial. As a result of this and other factors that differ from trial to trial, the trial-to-trial results vary, even though the underlying assumptions (in this case, the proportion of animals sent to each type of rendering facility on average) remain the same. Because many of the underlying assumptions are likewise uncertain, this assessment includes sensitivity analyses (see Section 2.3). For example, the 95th percentile estimate for potential human exposure in the base case provides an upper end estimate for this parameter assuming the base case assumptions are valid. However, the sensitivity analyses describe the range of predictions for the number of BSE cases and potential human exposure values associated with alternative plausible assumptions.

Further documentation of the Appendix 2 tables appears in Appendix 3C of Cohen *et al.* (1), although there is one change to the tables in Appendix 2A. Added to the values listed under the "Epidemic Statistics" heading, these tables now list an estimate of R_0, the epidemic's basic reproduction rate (14). Essentially, the value of R_0 is the average number of animals that become infected as the result of each new infected case. If R_0 is greater than 1.0, the prevalence of the disease tends to grow over time. If it is smaller than 1.0, prevalence tends to decrease over time

and eventually, the disease dies out. Section 1.2 of Gray and Cohen (15) explains the estimation of R_0. In brief, this value is estimated as the number of animals that become infected with BSE (excluding the infected animals introduced through import) divided by the number of BSE-infected animals that die during the simulation.

Tables 6a and 6b summarize key results for the base case and sensitivity analyses, showing how alternative (pessimistic) assumptions affect the predicted number of additional new cases of BSE and total human exposure to the BSE agent over the 20-year simulation period.

Table 6a
Total Number of New Infected Cases of BSE During the 20 Years Simulation Period

Scenario	Mean	Percentiles				
		5th	25th	50th	75th	95th
Base Case	21	12	16	19	22	30
S1 – Mislabel and contam.	21	12	16	19	22	30
S2 – Misfeeding	23	12	16	19	23	42
S3 – Render reduction factor	21	12	16	19	23	30
S4 – Poultry litter	22	12	16	19	23	38
S5 – Canadian BSE Prevalence	120	92	100	110	120	180
S6 – All assumptions	150	99	110	130	160	270

Table 6b
Total Potential Human Exposure to BSE (Cattle Oral ID$_{50}$s) During the 20 Year Simulation Period

Scenario	Mean	Percentiles				
		5th	25th	50th	75th	95th
Base Case	45	1.6×10^{-5}	0.0056	0.041	0.83	260
S1 – Mislabel and contam.	48	7.9×10^{-6}	0.0054	0.041	0.78	260
S2 – Misfeeding	45	1.2×10^{-5}	0.0062	0.044	1.0	260
S3 – Render reduction factor	48	9.6×10^{-6}	0.0055	0.041	0.83	260
S4 – Poultry litter	45	1.6×10^{-5}	0.0060	0.044	0.92	260
S5 – Canadian BSE Prevalence	260	0.20	2.1	60	260	770
S6 – All assumptions	290	0.26	3.1	120	270	840

The base case results (see Tables 6a, 6b, and Section 1 of Appendices 2A and 2B) indicate that over a 20-year period, imports of cattle from Canada are expected to produce a total of 21 BSE-infected cattle in the U.S. (5th percentile = 12 cases and 95th percentile = 30 cases). The simulation predicts that the vast majority of these cases will be imported, while approximately 10% (2.1 cases expected over 20 years, 5th percentile = 0 cases, 95th percentile = 6

cases) will represent secondary cases resulting from exposure of cattle in the U.S. to BSE from the imported cattle. The relatively small number of predicted native U.S. cases reflects the relatively small estimated R_0 value (mean of 0.044, 5th percentile = 0, 95th percentile = 0.25). Population potential human exposure to the BSE agent is expected to total 45 cattle oral ID_{50}s over 20 years.

The sensitivity analysis results indicate that the assumed Canadian BSE prevalence rate is by far the most important source of uncertainty. Use of the pessimistic value for this assumption increases the expected total number of BSE cases from 21 to 120, and the expected number of secondary BSE cases from 2.1 to 12. Total predicted potential human exposure increases from an expected value of 45 cattle oral ID_{50}s over 20 years to 260 cattle oral ID_{50}s over that time period.

Among the other uncertain assumptions analyzed, the misfeeding rate and the proportion of poultry litter used in cattle feed are most influential, although neither of these is nearly as influential as the assumed prevalence of BSE in Canada. Simultaneous use of pessimistic values for all five uncertain assumptions described here results in a total of 150 BSE cases in the U.S., 42 of which are native to this country. Mean human exposure to the BSE agent increases to 290 cattle oral ID_{50}s over 20 years.

The R_0 parameter is an important aggregate measure of the U.S. agricultural system's robustness in the face of potential disease introductions because it indicates whether BSE prevalence will tend to grow or whether BSE will die out over time. The average R_0 value for the base case analysis was 0.044. More importantly, the 95th percentile value for this parameter was 0.25, indicating that if the base case assumptions are valid, it is very unlikely that the disease's prevalence will grow over time independently of the import of additional infectivity. That is, it is very unlikely that $R_0 > 1$. Even simultaneous use of pessimistic values for all five assumptions evaluated here yielded the prediction that $R_0 > 1$ is unlikely. Overall, these results indicate that any plausible introduction of BSE into the U.S. results in only a limited spread of the disease among cattle in this country. Equivalently, the results indicate that in the absence of a continual introduction of BSE into the U.S., its prevalence will decrease over time, eventually leading to its elimination. From this prediction, it follows that potential human exposure to the BSE agent would be limited.

References

(1) Cohen JT, Duggar K, Gray GM, Kreindel S. Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States: Report to the U.S. Department of Agriculture (revised October, 2003). 2003. Boston, MA, Harvard Center for Risk Analysis. Available at: http://www.hcra.harvard.edu/peer_reviewed_analysis.html.

(2) Cohen JT, Duggar K, Gray GM et al. A simulation model for evaluating the potential for spread of bovine spongiform encephalopathy to animals or to people. In: Nunnally B, Krull I, editors. Prions and Mad Cow Disease. New York: Marcel Dekker, Inc., 2003.

(3) Cohen JT, Gray GM. Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update: Phase IA. Prepared for USDA/FSIS. 2005. Boston, Harvard Center for Risk Analysis.

(4) European Commission. Health & Consumer Protection Directorate-General Report on the Monitoring and Testing of Ruminants for the Presence of Transmissible Spongiform Encephalopathy in the EU in 2003, Including the Results of the Survey of Prion Protein Genotypees in Sheep Breeds. Report No. 04-D-420525. 2004.

(5) European Food Safety Authority. Opinion of the Scientific Panel on Biological Hazards of the European Food Safety Authority on BSE risk from bovine tonsil and consumption of bovine tongue. EFSA Journal 2004; 41:1-4.

(6) Wells GAH, Spiropoulos J, Hawkins SAC, Ryder SJ. Pathogenesis of experimental bovine spongiform encephalopathy: preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle. Veterinary Record 2005; 156:401-407.

(7) Cohen JT, Duggar K, Gray GM, Kreindel S. Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States: Report to the U.S. Department of Agriculture. 2001. Boston, MA, Harvard Center for Risk Analysis. Available at: http://www.hcra.harvard.edu/BSE_analysis.html.

(8) U.S.Food and Drug Administration. March 2005 Update on Feed Enforcement Activities to Limit the Spread of BSE. 2005. Center for Veterinary Medicine. Available at: http://www.fda.gov/cvm/CVM_Updates/BSE0305.htm.

(9) U.S.Food and Drug Administration. Update on Ruminant Feed (BSE) Enforcement Activities (April 15, 2002). 2002. Center for Veterinary Medicine. Available at: http://www.fda.gov/cvm/bseap02.htm.

(10) U.S.Food and Drug Administration. June 20 2005 Update on Feed Enforcement Activities to Limit the Spread of BSE. 2005. Center for Veterinary Medicine. Available at: http://www.fda.gov/cvm/bse0605.htm.

(11) Informa Economics. An Economic and Environmental Assessment of Eliminating Specified Risk Materials and Cattle Mortalities from Existing Markets. 2004. McLean, VA, Prepared for the National Renderers Association.

(12) U.S.Food and Drug Administration. Environmental Assessment for the IFR on Use of Materials Derived from Cattle in Human Food and Cosmetics. 2004. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/04n-0081-ea00001.pdf.

(13) U.S.Food and Drug Administration. 21 CFR 589. Substances prohibited from use in animal food or feed; proposed rule. Federal Register 2005; 70(193):58570-58601.

(14) Anderson RM, May RM. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, 1991.

(15) Gray GM, Cohen JT. Response to Comments Submitted in Response to USDA's Proposed Rule on Importing Beef and Beef Products from Canada. 2004. Boston, MA, Harvard Center for Risk Analysis.

Appendix 1 Base Case Parameter File Changes From Earlier Analysis

Appendix 2 Detailed Simulation Output

Appendix 3 Numerical Stability of Simulation Output

Base Case
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	22	30
Total Infected w/o Imports	2.1	0	0	0	0	6
Total Clinical	0.67	0	0	0	1	2
Probability Infected > 0 at End	0.12	0	0	0	0	1
R_0 Parameter	0.044	0	0	0	0	0.25
Mode of Infection						
Maternal	0.094	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2	0	0	0	0	6
Blood	0.0099	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	17	10	13	16	19	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.7	0	1	1	2	4
ID50 Sources						
From Slaughter	9,700	2,100	3,200	6,300	14,000	25,000
From Death on Farm	11,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	120	320	760	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,400	13,000	22,000	34,000
4 To NP MBM - Contamination	0.0028	0	0	0	0	0
5 To NP MBM - Mislabeling	44	0	0	0	2.6	51
6 Out After Rendering	110	0	0	2.6	26	280
7 To Prohibited Feed	900	33	100	280	1,100	2,500
8 To NP Feed - Misdirected	670	10	58	150	550	2,100
9 To NP Feed - Contamination	0.00095	0	0	0	0	0
10 To NP Feed - Mislabeling	39	0	0	0	0.8	50
11 To Blood	0.63	0	0.000042	0.0033	0.19	3.6
12 Out After Feed Production	1,600	110	290	680	1,400	10,000
13 Misfed to Cattle	12	0	0	0	0	26
14 Total to Cattle	31	0	0	0	0.3	28
15 Total Potential to Humans	45	0.000016	0.0056	0.041	0.83	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	13	0	0	0	0	0
Spinal Cord	4.2	0	0	0	0	0
Blood	0.033	0	0	0	0	0.00027
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	3.9E-7	0	0	0	0	0
Contaminated Muscle Meat	0.16	2.8E-7	0.000075	0.0021	0.023	1.4
AMR	0.64	0	0	0.00098	0.0076	0.26
Beef on Bone	1.2	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.6	0	0	0	0	0
Tonsils	0.026	0	0	0	0	0.025

Sensitivity Analysis 1
Pessimistic Assumptions for Mislabeling and Contamination
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	22	30
Total Infected w/o Imports	2.3	0	0	0	0	7
Total Clinical	0.72	0	0	0	1	2
Probability Infected > 0 at End	0.12	0	0	0	0	1
R_0 Parameter	0.049	0	0	0	0	0.27
Mode of Infection						
Maternal	0.095	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2.2	0	0	0	0	6
Blood	0.01	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	17	10	13	16	19	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.8	0	1	1	2	4
ID50 Sources						
From Slaughter	9,600	2,000	3,200	6,000	14,000	25,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	110	310	750	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,300	13,000	22,000	35,000
4 To NP MBM - Contamination	0.0036	0	0	0	0	0.0026
5 To NP MBM - Mislabeling	56	0	0	0.2	26	230
6 Out After Rendering	100	0	0	2.6	26	280
7 To Prohibited Feed	900	31	94	280	1,100	2,500
8 To NP Feed - Misdirected	700	10	57	150	540	2,100
9 To NP Feed - Contamination	0.012	0	0	0	0	0.026
10 To NP Feed - Mislabeling	46	0	0	0	2.6	100
11 To Blood	0.63	0	0.00004	0.0028	0.18	3.7
12 Out After Feed Production	1,600	110	290	700	1,400	10,000
13 Misfed to Cattle	14	0	0	0	0	26
14 Total to Cattle	37	0	0	0	1.2	30
15 Total Potential to Humans	48	7.9E-6	0.0054	0.041	0.78	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	16	0	0	0	0	0
Spinal Cord	4.9	0	0	0	0	0
Blood	0.026	0	0	0	0	0.00031
Distal Ileum	24	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.00015	0	0	0	0	0
Contaminated Muscle Meat	0.15	1.9E-7	0.000073	0.0018	0.022	0.76
AMR	0.7	0	0	0.00098	0.0076	0.28
Beef on Bone	0.81	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.56	0	0	0	0	0
Tonsils	0.026	0	0	0	0	0.016

Sensitivity Analysis 2
Pessimistic Assumptions for Misfeeding
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	23	12	16	19	23	42
Total Infected w/o Imports	4.2	0	0	0	1	21
Total Clinical	0.95	0	0	0	1	3
Probability Infected > 0 at End	0.16	0	0	0	0	1
R_0 Parameter	0.082	0	0	0	0.059	0.56
Mode of Infection						
Maternal	0.12	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	4.1	0	0	0	1	21
Blood	0.011	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	19	10	14	17	20	33
Die on Farm - Render	1.5	0	0	1	2	4
Die on Farm - No Render	2	0	1	1	2	5
ID50 Sources						
From Slaughter	10,000	2,000	3,300	6,700	14,000	25,000
From Death on Farm	13,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,800	120	320	790	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	16,000	2,000	4,500	13,000	22,000	40,000
4 To NP MBM - Contamination	0.0023	0	0	0	0	0
5 To NP MBM - Mislabeling	42	0	0	0	2.6	51
6 Out After Rendering	110	0	0	2.6	26	280
7 To Prohibited Feed	970	33	100	290	1,100	3,100
8 To NP Feed - Misdirected	690	12	59	160	570	2,100
9 To NP Feed - Contamination	0.0014	0	0	0	0	0
10 To NP Feed - Mislabeling	36	0	0	0	2.6	53
11 To Blood	0.64	0	0.000044	0.0035	0.2	3.8
12 Out After Feed Production	1,600	110	290	700	1,500	10,000
13 Misfed to Cattle	45	0	0	0	2.6	100
14 Total to Cattle	64	0	0	0.0015	5.1	130
15 Total Potential to Humans	45	0.000012	0.0062	0.044	1	260
16 Eliminated by AM Inspector	4,400	0	0	0	10,000	20,000
Human Exposure						
Brain	12	0	0	0	0	0
Spinal Cord	4.1	0	0	0	0	0
Blood	0.035	0	0	0	0	0.00044
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	4.8E-6	0	0	0	0	0
Contaminated Muscle Meat	0.16	2.8E-7	0.000092	0.003	0.028	1.4
AMR	0.68	0	0	0.00067	0.007	0.28
Beef on Bone	1.2	0	0	0.00036	0.0077	0.34
Trigeminal Ganglia	0.75	0	0	0	0	0
Tonsils	0.027	0	0	0	0	0.51

Sensitivity Analysis 3
Pessimistic Assumptions for Render Reduction Factor
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	21	12	16	19	23	30
Total Infected w/o Imports	2.4	0	0	0	0	7
Total Clinical	0.68	0	0	0	1	2
Probability Infected > 0 at End	0.13	0	0	0	0	1
R_0 Parameter	0.053	0	0	0	0	0.28
Mode of Infection						
Maternal	0.094	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	2.3	0	0	0	0	7
Blood	0.01	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	18	10	14	16	20	26
Die on Farm - Render	1.3	0	0	1	2	3
Die on Farm - No Render	1.7	0	1	1	2	4
ID50 Sources						
From Slaughter	9,700	2,100	3,200	6,100	14,000	25,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,800	180	410	970	1,600	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	15,000	2,000	4,300	13,000	22,000	35,000
4 To NP MBM - Contamination	0.0027	0	0	0	0	0
5 To NP MBM - Mislabeling	45	0	0	0	2.6	56
6 Out After Rendering	98	0	0	2.6	26	280
7 To Prohibited Feed	930	56	140	330	1,100	2,500
8 To NP Feed - Misdirected	720	29	84	190	650	2,100
9 To NP Feed - Contamination	0.0014	0	0	0	0	0
10 To NP Feed - Mislabeling	41	0	0	0	2.6	51
11 To Blood	0.64	0	0.000038	0.0029	0.18	3.7
12 Out After Feed Production	1,700	160	380	860	1,600	10,000
13 Misfed to Cattle	12	0	0	0	0	26
14 Total to Cattle	30	0	0	0	0.48	48
15 Total Potential to Humans	48	9.6E-6	0.0055	0.041	0.83	260
16 Eliminated by AM Inspector	4,200	0	0	0	10,000	20,000
Human Exposure						
Brain	15	0	0	0	0	0
Spinal Cord	5.9	0	0	0	0	0
Blood	0.038	0	0	0	0	0.00026
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	2.6E-6	0	0	0	0	0
Contaminated Muscle Meat	0.15	1.9E-7	0.000074	0.0021	0.023	1.4
AMR	0.74	0	0	0.00084	0.0072	0.25
Beef on Bone	0.83	0	0	0.00036	0.0077	0.31
Trigeminal Ganglia	0.49	0	0	0	0	0
Tonsils	0.024	0	0	0	0	0.016

Sensitivity Analysis 4
Pessimistic Assumptions for Recycling of Chicken Litter
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	22	12	16	19	23	38
Total Infected w/o Imports	3.9	0	0	0	1	17
Total Clinical	0.91	0	0	0	1	2
Probability Infected > 0 at End	0.15	0	0	0	0	1
R_0 Parameter	0.078	0	0	0	0.056	0.52
Mode of Infection						
Maternal	0.12	0	0	0	0	1
Spontaneous	0	0	0	0	0	0
Protein	3.8	0	0	0	1	17
Blood	0.011	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	19	10	14	17	20	31
Die on Farm - Render	1.4	0	0	1	2	4
Die on Farm - No Render	2	0	1	1	2	5
ID50 Sources						
From Slaughter	10,000	2,100	3,300	6,800	14,000	26,000
From Death on Farm	12,000	0	0	10,000	20,000	30,000
Disposition of ID50s						
1 To Prohibited MBM	1,700	120	320	790	1,500	10,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	16,000	2,000	4,500	13,000	22,000	39,000
4 To NP MBM - Contamination	0.0012	0	0	0	0	0
5 To NP MBM - Mislabeling	41	0	0	0	2.6	54
6 Out After Rendering	95	0	0	2.6	26	280
7 To Prohibited Feed	920	33	100	290	1,100	2,700
8 To NP Feed - Misdirected	720	13	59	160	590	2,200
9 To NP Feed - Contamination	0.0026	0	0	0	0	0
10 To NP Feed - Mislabeling	40	0	0	0	2.6	51
11 To Blood	0.67	0	0.000046	0.0033	0.2	3.8
12 Out After Feed Production	1,600	110	290	700	1,500	10,000
13 Misfed to Cattle	18	0	0	0	0	26
14 Total to Cattle	63	0	0	0.00032	3.1	110
15 Total Potential to Humans	45	0.000016	0.006	0.044	0.92	260
16 Eliminated by AM Inspector	4,500	0	0	0	10,000	20,000
Human Exposure						
Brain	13	0	0	0	0	0
Spinal Cord	5	0	0	0	0	0
Blood	0.031	0	0	0	0	0.0004
Distal Ileum	25	0	0	0	0	260
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	3.7E-7	0	0	0	0	0
Contaminated Muscle Meat	0.15	2.8E-7	0.000074	0.0025	0.028	1
AMR	0.69	0	0	0.00098	0.0072	0.25
Beef on Bone	0.94	0	0	0.00036	0.0077	0.32
Trigeminal Ganglia	0.66	0	0	0	0	0
Tonsils	0.027	0	0	0	0	0.51

Sensitivity Analysis 5
Pessimistic Assumption for Canadian BSE Prevalence
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	120	92	100	110	120	180
Total Infected w/o Imports	12	0	0	2	8	75
Total Clinical	3.8	0	1	3	4	13
Probability Infected > 0 at End	0.52	0	0	1	1	1
R_0 Parameter	0.075	0	0	0.021	0.067	0.42
Mode of Infection						
Maternal	0.54	0	0	0	1	2
Spontaneous	0	0	0	0	0	0
Protein	11	0	0	2	7	73
Blood	0.062	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	100	79	88	96	110	140
Die on Farm - Render	6.9	2	5	6	8	14
Die on Farm - No Render	9.6	4	7	9	11	18
ID50 Sources						
From Slaughter	61,000	30,000	46,000	59,000	74,000	98,000
From Death on Farm	63,000	20,000	40,000	60,000	80,000	120,000
Disposition of ID50s						
1 To Prohibited MBM	9,200	2,700	4,500	6,400	14,000	23,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	85,000	44,000	64,000	80,000	99,000	140,000
4 To NP MBM - Contamination	0.0089	0	0	0	0	0.0026
5 To NP MBM - Mislabeling	220	0	2.6	26	77	1,000
6 Out After Rendering	530	5.1	42	100	360	1,400
7 To Prohibited Feed	5,000	970	2,000	3,200	5,300	14,000
8 To NP Feed - Misdirected	3,700	580	1,400	2,300	3,700	13,000
9 To NP Feed - Contamination	0.0098	0	0	0	0	0.0026
10 To NP Feed - Mislabeling	220	0	2.6	26	57	1,000
11 To Blood	3.7	0.021	0.45	1.8	5.1	14
12 Out After Feed Production	8,700	2,600	4,200	6,100	13,000	22,000
13 Misfed to Cattle	72	0	0	0.08	26	260
14 Total to Cattle	180	0.000034	2.3	26	51	1,000
15 Total Potential to Humans	260	0.2	2.1	60	260	770
16 Eliminated by AM Inspector	29,000	0	20,000	30,000	40,000	60,000
Human Exposure						
Brain	76	0	0	0	0	36
Spinal Cord	28	0	0	0	0	14
Blood	0.18	0	0	0	0.00036	0.69
Distal Ileum	140	0	0	0.01	260	510
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.000037	0	0	0	0	0
Contaminated Muscle Meat	0.86	0.0089	0.045	0.19	1.4	3.4
AMR	4.2	0.0028	0.017	0.071	0.37	10
Beef on Bone	6.3	0.0019	0.017	0.072	0.38	22
Trigeminal Ganglia	3.1	0	0	0	0	1.4
Tonsils	0.15	0	0	0	0.51	0.51

Sensitivity Analysis 6
Pessimistic Assumptions from Sensitivity Analyses 1 to 5
50,000 Simulation Trials

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	150	99	110	130	160	270
Total Infected w/o Imports	42	2	8	17	53	160
Total Clinical	7.4	0	2	3	7	29
Probability Infected > 0 at End	0.74	0	0	1	1	1
R_0 Parameter	0.23	0.018	0.071	0.14	0.35	0.63
Mode of Infection						
Maternal	0.95	0	0	0	1	4
Spontaneous	0	0	0	0	0	0
Protein	41	1	8	17	53	160
Blood	0.067	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	120	84	97	110	130	200
Die on Farm - Render	9.6	3	5	8	11	24
Die on Farm - No Render	13	5	8	10	15	32
ID50 Sources						
From Slaughter	5.8E174	32,000	49,000	63,000	80,000	110,000
From Death on Farm	77,000	21,000	50,000	61,000	90,000	180,000
Disposition of ID50s						
1 To Prohibited MBM	5.8E172	3,400	5,500	8,000	16,000	29,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	5.8E174	46,000	67,000	87,000	110,000	200,000
4 To NP MBM - Contamination	0.038	0	0	0.000044	0.026	0.1
5 To NP MBM - Mislabeling	390	12	54	100	310	1,200
6 Out After Rendering	680	28	83	190	610	2,000
7 To Prohibited Feed	5.8E172	1,300	2,600	4,000	7,300	17,000
8 To NP Feed - Misdirected	4,700	820	1,800	2,900	4,800	15,000
9 To NP Feed - Contamination	0.088	0	0	0.0008	0.026	0.26
10 To NP Feed - Mislabeling	330	0.0029	26	52	160	1,100
11 To Blood	4.1	0.028	0.55	2.1	5.8	15
12 Out After Feed Production	5.8E172	3,200	5,100	7,400	15,000	26,000
13 Misfed to Cattle	300	0	26	51	130	1,100
14 Total to Cattle	640	26	56	130	390	2,200
15 Total Potential to Humans	290	0.26	3.1	120	270	840
16 Eliminated by AM Inspector	32,000	10,000	20,000	30,000	40,000	70,000
Human Exposure						
Brain	89	0	0	0	0	75
Spinal Cord	31	0	0	0	0	15
Blood	0.2	0	0	0	0.00063	0.83
Distal Ileum	150	0	0	8	260	510
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.000016	0	0	0	0	0
Contaminated Muscle Meat	0.95	0.011	0.052	0.25	1.5	3.7
AMR	4.1	0.003	0.018	0.075	0.4	10
Beef on Bone	6.5	0.0022	0.017	0.075	0.47	22
Trigeminal Ganglia	3.5	0	0	0	0	3
Tonsils	0.16	0	0	0	0.51	0.53