Harvard Risk Assessment of Bovine Spongiform Encephalopathy Update
Phase IA

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Executive Summary

In December 2003, the United States Department of Agriculture (USDA) announced the discovery of a cow with bovine spongiform encephalopathy (BSE or "mad cow disease") in Washington State. Shortly thereafter, the Secretary of Agriculture announced several new steps designed to further reduce the risk that meat from affected animals would reach humans. Following that time, the Food and Drug Administration (FDA) considered new rules to help prevent the spread of BSE among cattle through contaminated animal feed. USDA Secretary Veneman convened a panel of international experts (formally known as the International Review Subcommittee of the Secretary's Advisory Committee on Foreign Animal and Poultry Diseases) to evaluate USDA's investigation of the BSE cow and BSE risk management measures and to advise USDA regarding possible further steps to address BSE in the United States.

We have used the simulation model developed by the Harvard Center for Risk Analysis (HCRA)(Cohen 2003a; Cohen 2003b) to evaluate the risk of BSE spreading among cattle in the U.S. and the potential for humans to be exposed to contaminated tissues. We model the response of the U.S. agricultural system for 20 years following the import of BSE-infected cattle. Key predictions made by the HCRA simulation model include the number of additional new cases of BSE that develop subsequent to the hypothetical introduction of infected animals into the U.S., the amount of BSE infective agent, measured as cattle oral ID_{50}s potentially available in human food, and the epidemic's basic reproduction rate, R_0. We present results as distributions reflecting the probabilistic nature of the model and the processes simulated. In addition, we conduct sensitivity analyses to evaluate the extent to which alternative assumptions shift these distributions.

Our updated "base case" represents the circumstances in the U.S. prior to the December 2003 discovery of the animal with BSE in Washington State. We then analyze the impact of risk management measures adopted by USDA, considered by FDA, or proposed by the International Review Subcommittee since that discovery[1].

[1] Just before the completion of this report, FDA published proposed rules governing the disposition of animals that die before being sent to slaughter. This analysis does not consider those proposals (see *Federal Register*, 70(193): 58569-58601, October 6, 2005).

Because of updated scientific data about infectious tissues, new information about compliance with the FDA feed controls, new assumptions regarding beef consumption, and structural changes in the model related to the disposition of non-ambulatory cattle, the base case projections differ slightly from those reported in our October, 2003 BSE Final Report (Cohen 2003a).

In addition, because of interest by the USDA Food Safety Inspection Service (FSIS) in how rule changes might affect the contribution of specific tissues to potential human exposure, we took steps to ensure greater numerical stability and more reliable representation of very low probability events. First, we conducted 750,000 trials of our standard base case scenario. That scenario models the U.S. cattle population and contamination of the human food supply for 20 years following the introduction of 10 BSE-infected cattle. For computational convenience, we then decreased the number of trials conducted (from 750,000 to 50,000 per scenario) and increased the number of infected animals introduced (from 10 to 500). Effectively, the numerical precision of a set of trials (expressed as the standard error of the mean divided by the estimated mean) depends on the product of the number of trials run and the number of infected animals introduced. Hence, the 50,000 trials of the base case with 500 infected animals introduced (25 million infected animals introduced in total) yielded even more precise estimates than the 750,000 trials of the base case with 10 infected animals introduced (7.5 million infected animals introduced in total).

Results indicate that the arithmetic mean of the resulting projections scaled by the ratio of the number of infected animals introduced (i.e., by 500 divided by 10, or 50). For example, the average number of new BSE infections increased from 3.5 animals to 180 animals (rounded to two significant digits), while the average contamination of human food increased from 75 cattle oral ID_{50}s to 3,800 ID_{50}s. Although the introduction of 500 BSE-infected cattle into the U.S. is extremely unlikely, this scenario allowed us to achieve satisfactory numerical stability using far less computer time. For this reason, all alternative scenarios and sensitivity analyses assumed the introduction of 500 infected cattle. In evaluating the results of the analyses in this report it should be recognized that the hypothetical introduction of 500 infected animals is simply for computational convenience and has no basis in any estimate of potential U.S. risk.

Sensitivity analysis identified the assumed rate of misfeeding (*i.e.*, the deliberate or accidental administration to cattle of feed containing ruminant protein and designated for non-

ruminants only) as an important parameter. Assigning the misfeeding rate the pessimistic value assumed in our sensitivity analysis increased the expected number of new BSE cases over 20 years by a factor of almost 15 compared to the base case (*i.e.*, from 180 to 2,600), while the mean value of R_0 increased from 0.24 in the base case to 0.89. However, information available to quantify the misfeeding rate at the time this analysis was conducted was extremely limited, leading to a wide range of estimates for this influential parameter. Better information would substantially narrow the range of plausible projections generated by the model. Lengthening the assumed incubation period by a factor of two decreased the mean number of newly BSE-infected cattle from 180 to 43 and potential human exposure from 3,800 cattle oral ID_{50}s to 1,900 cattle oral ID_{50}s. Other parameters evaluated as part of the sensitivity analysis (mislabeling and contamination rates, render reduction factors, beef on bone consumption rates, and the success of *antemortem* inspection at detecting clinically ill BSE cattle) were far less influential.

We found that the food safety measures enacted by USDA all reduce potential human exposure to BSE infectivity but have little effect on spread of BSE in the cattle population. Removing non-ambulatory ("downer") cattle from the human food supply reduces predicted potential human exposure by about 3% (leaving a mean of 3,700 cattle oral ID50s). Removing high risk tissues, often called specified risk materials or SRMs, from animals over 30 months of age almost completely eliminates potential human exposure, reducing it to 11 cattle oral ID_{50}s. Prohibiting only the use of advanced meat recovery (AMR, derived from the skull and backbone) on animals over 30 months of age reduces potential human exposure by approximately two-fifths to 2,200 ID_{50}s. It is worth noting that these are relative reductions to what is already a small risk in absolute terms, especially in light of the fact that these simulations reflect the assumed introduction of 500 infected cattle into the U.S. None of the combined measures yielded substantial improvements over their components.

We evaluated two measures under consideration by FDA, including a prohibition on the use of ruminant blood in ruminant feed, and the requirement that plants producing both prohibited material (*i.e.*, ruminant-derived material) and non-prohibited material use dedicated production lines. Our analysis indicates that neither of these actions would have much impact on the spread of BSE. Our earlier report (Cohen 2003a) concluded that blood contributes relatively little to the spread of BSE. Similarly, our earlier work suggests that cross-contamination is a relatively minor factor.

The International Review Subcommittee convened by Secretary Veneman has suggested the possibility of a ban on specified risk material from animals 12 months and older for both human food and animal feed. We evaluate the impact of this ban assuming perfect compliance. Our analysis suggests that this measure is extremely effective at reducing potential human exposure, decreasing it by more than 99% relative to the base case. Because we assumed that the ban also removes SRMs from dead stock prior to their rendering, the measure achieves a substantial reduction in the spread of BSE among cattle, decreasing the number of new infected BSE cases in the U.S. to 35 from 180. We predict that another suggestion made by this group, the removal of all animal-derived protein from cattle feed, would decrease the number of new BSE cases from 180 to 170 over 20 eyears. The remaining cases result primarily from misfeeding of rations containing ruminant proteins (feed intended for other species), to cattle. This measure has a small predicted impact on potential human exposure.

Overall, it is clear that by eliminating the most BSE-infectious tissue from human food, specified risk material bans have a substantial impact on potential human exposure. Eliminating this material from cattle feed can have an important impact on the spread of BSE among cattle if steps are taken to ensure that such bans also cover dead stock. It is important to note that we have not systematically evaluated all possible SRM bans (*e.g.*, prohibitions that set cutoffs at different ages than those evaluated here). Nor have we evaluated the potential risks resulting from the disposal of SRMs and other costs associated with these bans.

1 Introduction

In December 2003, the United States Department of Agriculture (USDA) announced the discovery of a cow with bovine spongiform encephalopathy (BSE or "mad cow disease") in Washington State. Shortly thereafter, the Secretary of Agriculture announced several new steps designed to further reduce the risk that meat from affected animals would reach humans. The Food and Drug Administration (FDA) also considered new rules to help prevent the spread of BSE among cattle through contaminated animal feed. In addition, USDA Secretary Veneman convened a panel of international experts (formally known as the International Review Subcommittee of the Secretary's Advisory Committee on Foreign Animal and Poultry Diseases) to evaluate USDA's investigation of the Washington state BSE case and BSE risk management measures, and to advise USDA regarding possible further steps to address BSE in the United States.

This paper describes the use of a simulation model developed by the Harvard Center for Risk Analysis (Cohen 2003a; Cohen 2003b) to evaluate the risk of BSE spreading among cattle in the U.S. and the potential for humans to be exposed to contaminated meat. Our "base case" represents the circumstances in the U.S. prior to the December 2003 discovery of the animal with BSE in Washington State. We then analyze the impact of measures adopted by USDA, considered by FDA, or proposed by the International Review Subcommittee since that discovery. Key predictions made by the Harvard simulation model include the number of additional new cases of BSE that develop subsequent to the hypothetical introduction of infected animals into the U.S., and the amount of BSE infective agent potentially available in human food.

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

2 Methods

In order to characterize the base case conditions in the U.S. prior to the December 2003 discovery of a BSE case in Washington state, several modifications were made to the Harvard simulation model used in earlier analyses (Cohen 2003a; Cohen 2003b). Section 2.1 details these modifications. In addition, we revised parameter assumptions to better characterize base

conditions in the U.S. Changes made to the base case assumptions (compared to the base case assumptions outlined by Cohen *et al.* (2003a)) appear in Section 2.2. Section 2.3 outlines the alternative scenarios included in this analysis for the purpose of evaluating policy changes adopted by USDA, considered by FDA, or proposed by the International Review Committee. Finally, Section 2.4 describes sensitivity analyses conducted for the purpose of characterizing the extent to which our findings depend on assumptions made for critical parameters.

Note that where possible, our base case assumptions are central estimates. In a few limited cases, information is so limited that development of a central estimate is not feasible. In these cases, we attempt to err on the side of using conservative assumptions, *i.e.*, assumptions that tend to overstate the spread of BSE and the extent that it will contaminate human food. Use of conservative assumptions does not compromise the overall findings of this report, namely that the spread of BSE and contamination of human food are limited. In any case, as described below, we resorted to conservative estimates only for assumptions known to have a limited impact on the simulation results.

2.1 Revisions to the Harvard Simulation Model

We have implemented four sets of changes to the Harvard simulation model for the purpose of this analysis. These include: 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); and changes to SRM inspection (Section 2.1.4); and addition of supplemental reports that detail contamination of human food by animal age and ambulatory status (Section 2.1.5)..

2.1.1 Ambulatory Status

USDA now prohibits the use of non-ambulatory animals for human food (see Section 2.3.1, below). In order to represent this policy in our model, along with others that may place restrictions on the use of these animals in feed, we have modified the simulation so that it tracks the ambulatory status of cattle infected with BSE. The simulation designates 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

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 and animal feed based on these two determinations, 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 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

We have added tonsils as a tissue category.

2.1.4 SRM Inspection

The original BSE simulation model (Cohen 2003a) 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 now removes infectivity from dead stock, as well.

2.1.5 Supplemental Reports

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 creates 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).

2.2 Base Case Assumptions

This section outlines changes made to the base case assumptions used in our earlier risk assessment (Cohen 2003a). 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), and 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).

Section 2.2.6 further discusses evaluation of the potential number of BSE-infected animals introduced into the U.S. .

Before proceeding to these subsections, we note that we have increased both the number of simulation trials and the number of infected animals introduced at the beginning of each trial in order to more precisely quantify the impact of measures that have a limited impact on the spread of BSE and the contamination of human food and to characterize the impact of such measures on BSE levels in specific tissue categories. In order to be consistent with past analyses, such as Cohen *et al.* (Cohen 2003a), we defined a base case scenario that postulates the introduction into the U.S. of 10 BSE-infected cattle. To achieve a sufficient degree of numerical precision for the purpose of evaluating the interventions considered in this report, our methodology called for 750,000 trials of this base case scenario[2]. In order to reduce the number of simulation trials necessary to achieve this level of precision, we increased the number of infected cattle introduced in the base case from 10 to 500 and decreased the number of trials from 750,000 to 50,000. Because the precision of the estimated mean values produced by the simulation depends on the number of infected cattle introduced multiplied by the number of trials, 50,000 trials with 500 infected animals introduced each time (25 million infected cattle in total) achieved precision exceeding that achieved by 750,000 trials with 10 infected animals introduced each time (7.5 million infected cattle in total). We recognize that an introduction of 500 infected cattle into the U.S. is very unlikely. However, simulation of 50,000 trials of 500 infected animals being introduced takes approximately one-tenth the time needed to run 750,000 trials of 10 infected animals being introduced.

Comparison of the two sets of base case scenarios confirmed that the means scaled in proportion to the number of infected cattle introduced. For example, the 10-infected animal version of the base case produced a mean of 3.5 newly infected cattle, whereas the corresponding figure for the 500-animal version of the base case was approximately 50 times greater (i.e., 180) (both values rounded to two significant digits). The mean estimated number of cattle oral ID_{50}s in human food also scaled by approximately a factor of 50 (75 in the 10-animal base case and 3,800 in the 500-animal version). It is important to realize that percentile estimates do not scale in a straight-forward manner. For example, the 95th percentile estimate for contamination of human

[2] Due to an error, 749,255 trails were run for the base case scenario, 99.9% of the total called for in our study design. This shortfall almost certainly has no meaningful impact on the precision of our results.

food amounts to 320 cattle oral ID_{50}s in the 10-animal version of the base case, while for the 500-animal version of the base case, this value is 8,700, a difference of around a factor of 30.

Because simulation of 50,000 trials involving the introduction of 500 infected cattle takes far less time than 750,000 trials involving the introduction of 10 infected animals, we used the 500-animal version of the base case and compared it to 500-animal versions of the sensitivity analysis scenarios and alternative scenarios considered in this report. In so doing, we recognize that the introduction of 500 infected animals into the U.S. is very unlikely.

2.2.1 Assignment of Ambulatory Status

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, we assume 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, we assume approximately 1 in 200 animals is nonambulatory. That is, we assume that P(NA) is 0.5% and hence that $P(NA \mid NS)$ is 0.5%. As explained in Section 3.3, we evaluate the importance of this assumption using sensitivity analysis.

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

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

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 surveillance data have been collected in Europe (European Commission 2004). However, the European surveillance data do not document ambulatory status. We have therefore investigated a range of values for $P(NA \mid S)$ ranging from 8% (base case) to as high as 100% (see Sensitivity Analysis 8).

2.2.2 *Antemortem* Inspection

Probability of passing inspection for non-BSE factors – For animals with normal ambulatory status, we use the pass probabilities used by Cohen *et al.* (Cohen 2003a). For non-ambulatory animals, we assume that 60% of the animals pass inspection (non-BSE factors only). There is admittedly very little information to help estimate this probability. The value of 60% reflects the assumptions that 1) 0.5% of all animals are non-ambulatory and that 2) 0.3% of all cattle are animals that are non-ambulatory but pass *antemortem* inspection anyway. Because both of these values are uncertain, their ratio of 60% is also very uncertain. In any case, the assumption that 60% of non-ambulatory animals pass *antemortem* inspection is likely to be conservative. In any case, Cohen *et al.* showed that the simulation results are not sensitive to assumptions about the performance of the *antemortem* inspector.

Probability that antemortem inspector will discover a clinical animal – Cohen *et al.* (2003a) assumed that the *antemortem* inspector passes (i.e., fails to catch) 10% of all animals with clinical signs of BSE. That is, we assumed 90% of identifies clinical animals with 90% probability. For this analysis, we assume 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, we assume 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 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. Non-ambulatory status does not affect the use of an animal for human food.

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.

2.2.3 Infectivity in Tonsils

Recent information suggests that bovine tonsils may carry BSE infectivity (European Food Safety Authority 2004). 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 (European Food Safety Authority 2004; Wells 2005)

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 (European Food Safety Authority 2004)). 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, 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)). Hence, the total infectivity in tonsils implied by the DNV calculations amounts to 0.2% of the total infectivity in the entire animal ($0.5 \div 250$ oral ID_{50}s).
We assume that the tonsils maintain this same fraction of infectivity throughout the BSE incubation period. In order to maintain the same total quantity of infectivity in an animal assumed in our earlier analysis, we have multiplied the tissue-specific fractions for other tissues at each age point by 99.8%.

2.2.4 Feed Ban Compliance Rates

This analysis uses the most recent 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 (Cohen 2001), 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[3] quantifies the number of facilities out of compliance with the feed rule and hence serves as a useful starting point for our analysis. However, because the U.S. FDA databases do not report the size of these facilities (*i.e.*, total material throughput), we have to make an assumption regarding the size of the non-compliant facilities compared to other facilities. For this purpose, we assume 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, we rely on data collected by FDA/CVM[4] prior to September, 2003. 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. In any case, 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 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 (U.S. Food and Drug Administration 2003) defines these terms[5].

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[3] (http://www.fda.gov/cvm/index/bse/bse_updates.htm) and the online database of current inspection status (http://www.accessdata3.fda.gov/BSEInspect)

[4] Compliance program implementation details can be found at http://www.fda.gov/cvm/index/cpg/7371-009.doc.

[5] 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

Table 1 reproduces the April 2002 FDA Update (U.S. Food and Drug Administration 2002), 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 Comingling (N)	Cited for Comingling 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

The parameters adopted for our analysis are highlighted in Table 1 and reproduced in Table 2 for the purpose of comparing them with assumptions made in our earlier risk assessment (Cohen 2003a).

material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented."

"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 provisions such as minor recordkeeping lapses and conditions involving non-ruminant feeds." (U.S. Food and Drug Administration 2003).

Table 2
Assumptions for Mislabeling and Contamination

Parameter	MBM Production			Feed Production		
	Base Case (2003)[(a)]	Worst Case (2003)[(a)]	Revised Worst Case[(b)]	Base Case (2003) [(a)]	Worst Case (2003) [(a)]	Revised Worst Case[(b)]
Probability of Contamination	14%	25%	1.8%	16%	16%	1.9%
Proportion of Prohibited Material Transferred to Non-Prohibited Material per Contamination Event	0.1%	1%	1%	0.1%	1%	1%
Mislabeling Probability	5%	10%	2.3%	5%	33%	4%

Notes:

(a) Values from Cohen et al. (2003a).
(b) Values developed for this assessment.

Although our base case parameter values reflect several conservative assumptions, the results of Sensitivity Analysis #1 indicate that even substantial modifications to these rates have at most a modest impact on the simulation results (see Section 3.3). 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

Cohen *et al.* (2003a) assumed that slaughter facilities do not produce bone in cuts of beef from animals over 24 months of age[6]. These cuts are potentially important because they may contain either spinal cord, dorsal root ganglia (DRG) or both. At the request of USDA, and based on the judgment of USDA personnel, we 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. We also assume that for all

[6] Discussed in Cohen et al., 2003 Appendix 1 at 2.18.3

animals, 30% of DRG is available for potential human exposure to in 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.

2.2.6 Number of BSE-Infected Animals Introduced into the U.S.

Cohen *et al.* (2003a) noted that it is difficult to quantitatively characterize likely introductions of BSE into the U.S. For that reason, they investigated a wide range of potential introductions, considering, for example, the introduction of between 1 and 500 BSE-infected animals into this country. The base case developed by Cohen *et al.* assumed the introduction of 10 BSE-infected animals. Many other scenarios described in that report also assumed the introduction of 10 BSE-infected animals, including all the sensitivity analysis scenarios, in order to facilitate comparison of the results.

In this analysis, we continue to assume the introduction of 10 BSE-infected animals at the beginning of the simulation. Although substantial additional surveillance and the discovery of two BSE-positive animals in the U.S. (one in Washington State in 2003 and one in Texas in 2005) helps us to better understand the range of plausible prevalence rates for BSE in the U.S., the range of possible prevalence values remains large relative to any central estimate value. Assuming that approximately 300,000 high risk animals have been tested, the discovery of these two cases yields a central value for the estimated BSE prevalence among animals that die or are slaughtered of 1 in 150,000. If it can validly be assumed that there are no BSE cases outside of the high risk population of approximately 450,000 animals identified by USDA (USDA Bovine Spongiform Encephalopathy (BSE) Surveillance Plan March 15, 2004, http://www.fas.usda.gov/dlp/BSE/bse.html -- accessed August 13, 2004), the central estimate for the total number of animals in the U.S. would be approximately 3, with a 95% confidence interval of approximately 1 to 11 (see (Jaynes 1976)).

Estimating the actual number of animals with BSE is complicated by the potential for there to be infected animals outside the high risk group identified by USDA, although the number of such animals that would test positive using even the best available tests is likely to be small (Cohen 2004). Additionally, the fact that the 2003 detected BSE case in Washington State was an animal native to Canada complicates the estimation of a prevalence rate for the U.S.

Because statistical estimates of the prevalence of BSE in the U.S. remain uncertain, we continue to assume the introduction of 10 BSE-infected animals at the beginning of the simulation scenarios considered here. Because most of the outcomes predicted by the simulation scale proportionally with the number of animals introduced (Cohen 2003a), our findings can be easily extrapolated to reflect alternative assumptions.

2.3 Alternative Scenarios

We divide the alternative scenarios considered into three categories: changes made by USDA since the discovery of the BSE case in Washington state (Section 2.3.1), changes considered by U.S. FDA (Section 2.3.2), and changes proposed by the International Review Committee (Section 2.3.3).

2.3.1 Changes Made by USDA

We consider three primary alternative scenarios, along with the three pairwise combinations of these alternatives.

- *USDA A* – Ban on slaughter for human consumption of all non-ambulatory disabled cattle (Federal Register: January 12, 2004 (Volume 69, Number 7 Pages 1861-1874)).
- *USDA B* – Prohibition for human consumption of brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column, and dorsal root ganglia of cattle 30 months of age or older, as well as small intestine and tonsils of all cattle (Federal Register: January 12, 2004 (Volume 69, Number 7 Page 1861-1874)).
- *USDA C* – Prohibition of production for human consumption of advanced meat recovery (AMR) product from vertebrae or skulls of cattle 30 months of age or older along with prohibition for human consumption of mechanically separated beef derived from cattle of all ages ([Federal Register: January 12, 2004 (Volume 69, Number 7 Pages 1874-1885].
- USDA A and USDA B
- USDA A and USDA C
- USDA B and USDA C.

2.3.2 Changes Considered by U.S. FDA

We evaluate the risk reduction that could be achieved by implementing regulations considered by FDA

- *FDA 1* – Ban on the use of ruminant blood in ruminant feed (cited in Federal Register: July 14, 2004 (Volume 69, Number 134 Pages 42287-42300).
- *FDA 2* – Requirement for dedicated lines for production of animal feeds containing prohibited (*i.e.*, ruminant derived) protein in facilities producing both prohibited and non-prohibited material (cited in Federal Register: July 14, 2004 (Volume 69, Number 134 Pages 42287-42300))

2.3.3 Changes Proposed by the International Review Committee

Next, we evaluate the risk reduction that could be achieved by implementation of two recommendations of the International Review Subcommittee of the Secretary's Advisory Committee on Foreign Animal and Poultry Diseases (Report of the Secretary's Advisory Committee on Foreign Animal and Poultry Diseases: Measures Relating to Bovine Spongiform Encephalopathy in the United States, http://www.fas.usda.gov/bse04.htm -- accessed August 13, 2004). These include:

- *Int Comm 1* – Exclusion from human food and animal feed of brain, spinal cord, and vertebral column from bovines 12 months of age and older and the entire intestine from cattle of all ages. Compliance is assumed to be perfect. We assume furthermore that the SRM restriction applies to both slaughtered cattle and dead cattle.
- *Int Comm 2* – Prohibition of all meat and bone meal in ruminant feed.

Because the simulation does not explicitly model all animal feed or even all cattle feed, there is no direct way to specify the second scenario described above. Instead, the model describes the flow of BSE infectivity contained in ruminant tissue. We therefore develop parameter assumptions that describe the impact of the prohibition considered here on the flow of ruminant protein. First, we assume that all MBM is produced by prohibited MBM producers (because there is no longer any such thing as non-prohibited MBM). We assume further that there can be no mislabeling of MBM as non-prohibited. On the other hand, we assume that prohibited MBM can be sent to a mixed feed producer, as in the base case. We also assume that the feed producer may still contaminate non-prohibited feed (mixed producers only) or that

prohibited feed may be mislabeled as non-prohibited (mixed and prohibited feed producers). For both of these sets of parameters, we use the base case assumptions in this scenario.

2.4 Sensitivity Analyses

As in the 2003 risk assessment (Cohen 2003a), we have conducted 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, the predicted number of new BSE cases over a 20 year period, and potential human exposure to the BSE agent during that same period.

The sensitivity analyses conducted here evaluate the impact of alternative assumptions for specific parameters identified as influential in the original analysis (Cohen 2003a). We also investigate the impact of changing assumptions for the *antemortem* inspection process because this part of the simulation has been substantially revised. Assumptions are deemed important sources of uncertainty only if they qualitatively influence the model's predicted results. For the base case scenario, the model already predicts that the spread of BSE among cattle and potential human exposure would be limited. Optimistic assumptions would not change this prediction qualitatively and hence need not be quantitatively analyzed. Instead, we investigate the impact of pessimistic values.

Sensitivity analyses include:

- *Sensitivity 1* – Mislabeling and contamination – We have revised the base case values for these parameters to take into account new data on compliance rates. The sensitivity analyses evaluate the impact of replacing these assumptions with the more pessimistic base case assumptions from Harvard's October, 2003 report. In particular, we increase the mislabeling rates to 5% for both MBM and feed production. We increase contamination rates increased to 14% (MBM production) and 16% (feed production).

- *Sensitivity 2* – Misfeeding – Misfeeding rate increased to 15%. This worst case value is the same as the worst case value used in Harvard's October, 2003 report.

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

- *Sensitivity 4* – Bone in beef use in human food – We increase the proportion of bone in beef potentially available for human consumption from its base case values to 100% (animals 0 to 23 months), 90% (animals 24 to 29 months), and 45% (animals 30 months or older).

- *Sensitivity 5 – Antemortem* inspection – We make the *antemortem* inspector less effective at identifying cattle with clinical BSE signs. The *antemortem* inspector detects 50% of animals with signs if they are ambulatory. If they are non-ambulatory, the *antemortem* inspector detects such animals with 25% probability.

- *Sensitivity 6* – Incubation period – we expand the incubation period distribution (detailed in Section 3.1.1.6 in Cohen *et al*. (2003a)) by doubling the value of each percentile. For example, the 5^{th} percentile is doubled from a base case value of 2.5 years to 5 years, the median is increased from a value of approximately 4 years to 8 years, and the 95^{th} percentile is increased from a value of 7 years to approximately 14 years.

- Sensitivity 7 – Non-ambulatory probability for animals with no clinical signs. We decrease this probability to zero from its base case value of 0.5% to determine if doing so has a substantial impact on either the number additional animals infected with BSE or potential human exposure to the BSE agent. This measure should increase risk by decreasing the probability that animals not showing clinical signs will be rejected at ante-mortem inspection.

- Sensitivity 8 – Non-ambulatory probability for animals <u>with</u> clinical signs. We increase this probability to 100% from its base case value of 8% to determine if doing so has a substantial impact on the results. This measure should increase risk because clinical signs in non-ambulatory animals are <u>less</u> likely to be detected at ante-mortem inspection than in ambulatory animals.

3 Results and Discussion

The quantitative results of our 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 by tissue type. Appendix 2B details potential human exposure by cattle age range and ambulatory status. Finally, Appendix 2C 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 results vary from trial to trial, even though the underlying assumptions (in this case, the proportion of animals sent to each type of rendering facility on average) remains the same. Because many of the underlying assumptions are likewise uncertain, we have conducted sensitivity analyses (see Section 2.4). Hence, for example, the 95th percentile estimate for potential human exposure for 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 potential human exposure values associated with alternative plausible assumptions.

Further documentation of the Appendix 2 tables appears in Appendix 3C of Cohen *et al.* (Cohen 2003a), although we note one change to the tables in Appendix 2A. In particular, under the "Epidemic Statistics" heading, these tables now list an estimate of R_0, the epidemic's basic reproduction rate (Anderson 1991). 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 (Gray 2004) explains how we estimated R_0. In brief, we estimate this value as the ratio of the number of animals that become infected with BSE (excluding the 10 infected animals introduced at the beginning of the simulation) divided by the number of BSE-infected animals that die during the simulation.

3.1 Base Case

3.1.1 Base Case with 10 BSE-Infected Animals Introduced: 750,000 Trials

Results from this analysis, using the revised version of the model, can be directly compared with results from previous analyses. Sections 2.1 and 2.2 described revisions to the model. Qualitatively, our findings here are the same as in our earlier analyses, with the results indicating that the spread of BSE in the U.S. cattle population would be limited, that BSE would be eradicated from the U.S. over time, and that potential human exposure to BSE-contaminated food would be low.

Our results indicate that the disease is unlikely to spread substantially among cattle in the U.S. Base case values for R_0 are far less than 1.0 (mean = 0.087 and the 95th percentile = 0.52). These values for R_0 suggest that BSE would be eliminated relatively quickly. Figure 1 in Section 1 of Appendix 2C illustrates this point.

We estimate total potential human exposure over 20 years following an introduction of 10 infected animals to average 75 cattle oral ID_{50}s. This total exceeds the corresponding estimate reported for the base case by Cohen *et al.* (Cohen 2003a), with part of the increase due to greater amounts of infectivity in bone-in-beef (see Section 2.2.5). Note that this value represents potential human exposure, and that the bone-in-beef category includes cuts like T-bone steaks with spinal cord and dorsal root ganglia that may, or may not, actually be consumed.

3.1.2 500 BSE-Infected Animals Introduced: 50,000 Trials

This analysis forms the basis for subsequent evaluations of risk management measures in this report. It also reflects model revisions described in Sections 2.1 and 2.2. Comparison of this analysis with the 10 animal version of the base case (Section 3.1.1) reveals that for the most part, mean estimates scale by a factor of 50 (note that in some cases, our practice of rounding to two significant digits slightly obscures this relationship). On the other hand, percentile estimates do not in general scale in this manner.

Under these conditions, the model predicts an average of 180 new BSE cases during the 20 years following introduction of 500 infected animals (95th percentile 400 new cases). Note that the mean is very close to 50 times greater than the mean estimated for the 10 animal introduction version of the base case. Values for R_0 are still far less than 1.0 (mean = 0.24, 95th percentile = 0.45). We estimate total potential human exposure during the 20 years following an introduction of 500 infected animals to average 3,800 cattle oral ID_{50}s (95th percentile of 8,700).

3.2 Alternative Scenarios

Tables 3a and 3b summarize key results for the alternative scenarios, showing how these scenarios affect the predicted number of additional new cases of BSE over 20 years and total human exposure to BSE-contaminated food.

Table 3a
Alternative Scenarios: Number of New Infected Cases of BSE in the 20 Years Following Introduction of 500 Infected Animals Into the U.S.

Scenario	Mean	5th	25th	50th	75th	95th
Base Case	180	33	98	160	240	400
USDA A	180	33	98	160	250	400
USDA B	180	33	97	160	240	400
USDA C	180	33	97	160	240	400
USDA A + B	180	33	97	160	240	400
USDA A + C	180	33	96	160	240	400
USDA B + C	180	33	98	160	240	400
FDA 1	180	33	98	160	240	400
FDA 2	180	33	97	160	240	400
International Committee 1	35	19	25	30	38	71
International Committee 2	170	32	92	150	230	390

Table 3b
Alternative Scenarios: Potential Human Exposure to BSE (Cattle Oral ID_{50}s) in the 20 Years Following Introduction of 500 Infected Animals Into the U.S.

Label	Mean	5th	25th	50th	75th	95th
Base Case	3,800	1,600	2,400	3,200	4,400	8,700
USDA A	3,700	1,600	2,400	3,100	4,400	8,500
USDA B	11	2.7	5.8	8.6	12	20
USDA C	2,200	450	960	1,600	2,600	7,000
USDA A + B	10	2.7	5.7	8.4	12	20
USDA A + C	2,200	450	950	1,600	2,600	7,100
USDA B + C	10	2.7	5.7	8.5	12	19
FDA 1	3,800	1,600	2,400	3,200	4,400	8,600
FDA 2	3,800	1,600	2,400	3,200	4,400	8,700
International Committee 1	9.8	2.7	5.7	8.5	12	22
International Committee 2	3,800	1,600	2,400	3,200	4,400	8,600

3.2.1 USDA Alternative Scenarios

USDA Alternative Scenario A - Ban on Non-Ambulatory Cattle to Human Food

Our analysis shows that the measure considered in this scenario has little effect on the spread of BSE within the cattle herd. The predicted mean number of new BSE cases during the 20 year period following the introduction of BSE into the U.S. is the same as the base case. The measure does reduce predicted potential human exposure, decreasing the mean number of cattle oral ID_{50}s available for potential human exposure from 3,800 in the base case to 3,700. The 95^{th} percentile decreases from 8,700 to 8,500 cattle oral ID_{50}s. This food safety measure has little effect on R_0.

USDA Alternative Scenario B - No SRMs From Animals 30 Months or Older

This measure has a substantial effect on the predicted potential human exposure to BSE infectivity, reducing this exposure from 3,800 to 11 cattle oral ID_{50}s. However, it has no effect on the spread of BSE among cattle. This food safety measure does not substantially influence the value of R_0.

USDA Alternative Scenario C - No AMR From Animals 30 Months or Older

The measures reflected in this scenario reduce the probability that technologies used to maximize removal of meat from bones will contaminate meat products with dorsal root ganglia. Our analysis finds no change in the mean estimated number of new BSE cases. On the other hand, this measure does have a notable impact on potential human exposure, decreasing total potential exposure from 3,800 cattle oral ID_{50}s in the base case to 2,200 cattle oral ID_{50}s in this scenario. The distribution of R_0 values is virtually identical to that estimated for the base case.

USDA Alternative Scenarios A + B

Combining the measures embodied in USDA scenarios A and b does not offer a substantial improvement over the measure embodied in USDA scenario B alone.

USDA Alternative Scenarios A + C

As with USDA Scenario C, we predict no change in the number of new BSE cases. Our results suggest that USDA Scenarios A and C combined have virtually the same effect as USDA Scenario C alone (mean human exposure of 2,200 cattle oral ID_{50}s in USDA Scenarios A and C combined, the same as in USDA Scenario C alone). The value of R_0 is unchanged.

USDA Alternative Scenarios B + C

We again predict that the number of new BSE cases in the 20 years following the introduction of BSE into the U.S. is virtually unaffected. The mean potential human exposure, however, is virtually eliminated, decreasing from 3,800 to 10 cattle oral ID_{50}s. The model predicts that R_0 would be unaffected by these measures.

3.2.2 FDA Alternative Scenarios

FDA Scenario 1 - Ban on Use of Ruminant Blood in Feed

We predict that this measure would have little effect on the spread of BSE among cattle. This result is expected given the limited number of cases attributable to contamination of blood meal in the base case over 20 years (mean of 0.5 cases out of 180). It should be noted that the base-case scenario assumes the infectivity in blood results from the deposition of emboli formed during the stunning process, rather than from the disease process itself. This assumption reflects the findings of pathogenesis studies using either mice or calves in transmission bioassays, none of which have detected the presence of the BSE agent in blood. Cohen *et al.* (Cohen 2001) evaluated the impact of assuming BSE infection does spread to the blood as part of the disease process. In that report, the assumption that the concentration of the agent in blood just equals the level of detection continued to yield a small number of BSE cases due to cattle consumption of blood meal (mean of 0.11 cases, 95^{th} percentile of 1.0 case in a scenario with introduction of 10 infected animals). If we were to make this assumption here, the predicted benefit of the measure embodied by FDA Scenario 1 would probably increase by a corresponding amount.

FDA Scenario 2 – Dedicated Production Lines in Rendering and Feed Production Facilities

FDA Scenario 2 has a small impact, eliminating the 0.17 cattle oral ID_{50}s that contaminate non-prohibited MBM and the 0.17 cattle oral ID_{50}s that contaminate non-prohibited feed during the 20 years following introduction of 500 BSE infected animals (see table in Section 1 of Appendix 2A).

3.2.3 International Review Subcommittee Scenarios

International Review Committee Scenario 1 – SRM Ban: Animals 12 Months and Older

Removing infectious tissues from both human food and animal feed, assuming that the ban effectively covers dead stock, and assuming perfect compliance, together have a substantial impact on both potential human exposure and the spread of BSE. Predicted new cases of BSE decreases from an average of 180 cases over 20 years to 35 cases. Of the remaining new BSE cases, only one-third result from exposure to contaminated animal feed, with the remaining two-thirds caused almost exclusively by maternal transmission. Potential human exposure decreases both because there are fewer BSE cases and because the measures remove infectious tissues from the human food supply. Average potential human exposure decreases by more than 99% from 3,800 cattle oral ID_{50}s to 10 ID_{50}. Reflecting the decrease in predicted new cases of BSE, the R_0 value drops from a mean of 0.24 in the base case to a mean of 0.065 in this scenario.

We note that this analysis assumes that the SRM ban is "perfect," *i.e.*, that there is no possibility that disposed of SRMs may contaminate feed and result in the spread of BSE. The potential for leaks in an SRM ban, as well as other factors, must be considered in evaluating the complete benefits of any specific measure.

International Review Committee Scenario 2 – Prohibition of all meat and bone meal in ruminant feed

While the measures embodied in this scenario aim to reduce the possibility of cross contamination, they do not address the potential for misfeeding of prohibited feed to ruminants. Because of dead stock may still be used to produce MBM, ruminant protein may still be present in that prohibited feed. Given these issues, it is not surprising that our analysis predicted only a

small decrease in the spread of BSE in this scenario relative to the base case (mean new cases decreased to 170 from 180). The mean value of R_0 remains unchanged at 0.24.

3.3 Sensitivity Analyses

Tables 4a and 4b summarize key results for the sensitivity analyses, showing how these scenarios affect the predicted number of additional new cases of BSE over 20 years and total human exposure to BSE-contaminated food.

Table 4a
Sensitivity Analyses: Number of New Infected Cases of BSE in the 20 Years Following Introduction of 500 Infected Animals Into the U.S.

Label	Mean	5th	25th	50th	75th	95th
Base Case	180	33	98	160	240	400
Sensitivity 1	200	38	110	180	270	440
Sensitivity 2	2,600	1,200	1,900	2,500	3,200	4,400
Sensitivity 3	240	38	130	210	330	530
Sensitivity 4	180	33	97	160	240	400
Sensitivity 5	190	36	100	170	260	420
Sensitivity 6	43	6	13	24	60	130
Sensitivity 7	180	33	97	160	240	400
Sensitivity 8	180	33	97	160	240	400

Table 4b
Sensitivity Analyses: Potential Human Exposure to BSE (Cattle Oral ID_{50}s) in the 20 Years Following Introduction of 500 Infected Animals Into the U.S.

Label	Mean	5th	25th	50th	75th	95th
Base Case	3,800	1,600	2,400	3,200	4,400	8,700
Sensitivity 1	3,800	1,600	2,400	3,300	4,500	8,700
Sensitivity 2	9,000	4,200	6,300	8,300	11,000	16,000
Sensitivity 3	4,000	1,700	2,500	3,400	4,700	8,800
Sensitivity 4	4,500	2,000	3,000	3,900	5,300	9,400
Sensitivity 5	6,600	3,000	4,300	5,700	7,900	13,000
Sensitivity 6	1,900	650	1,100	1,600	2,200	4,400
Sensitivity 7	3,800	1,600	2,400	3,200	4,400	8,700
Sensitivity 8	3,800	1,600	2,400	3,200	4,500	8,800

Sensitivity 1 – Pessimistic MBM/Feed Production Mislabeling and Contamination Assumptions

This scenario replaces assumptions for mislabeling contamination rates derived using recent FDA compliance data (see Section 2.2.4) with the more pessimistic compliance rates used in the base case in our earlier analyses (Cohen 2001; Cohen 2003a). The more pessimistic assumptions have a modest impact on the predicted spread of BSE, increasing the predicted average number of new cases over 20 years following introduction of 500 BSE infected cattle from 180 to 200.

Sensitivity 2 – Pessimistic Misfeeding Assumptions

Cohen *et al.* (Cohen 2001; Cohen 2003a) have pointed out that the predicted spread of BSE is particularly sensitive to assumptions about the rate at which prohibited feed, containing ruminant protein, is inappropriately fed to cattle. The range of plausible values for this parameter remains very uncertain, as no new information has become available in the last three years. We therefore continue to use the worst case value of 15% used in our earlier analyses. Gray and Cohen discuss this parameter further (Gray 2004).

As expected, increasing the assumed misfeeding rate from its base case value of between one and two percent to approximately one in seven batches of prohibited feed causes the simulation model to predict that BSE spreads to a substantially greater degree. The mean number of new cases predicted increases to 2,600 with a 95^{th} percentile of 4,400. Potential human exposure increases from an average of 3,800 cattle oral ID_{50}s in the base case to 9,000 in this analysis (95^{th} percentile 16,000). Significantly, although the predicted mean value for R_0 is below 1 (mean of 0.89), the 95^{th} percentile value for R_0 value is 1.0, suggesting that if BSE were introduced into the U.S., its prevalence might grow over time, albeit very slowly. It is important to note that some measures suggested by the International Review Subcommittee (International Review Subcommittee Scenarios 1 and 2) reduce the influence of misfeeding by reducing the amount of infectivity in prohibited feed.

Sensitivity 3 – Pessimistic Render Reduction Factor Assumptions

Different rendering processes inactivate BSE to different degrees. This scenario uses the worst case values from Cohen *et al.* (2003a) for the amount of material rendered using various technologies. The model predicts that these changes would increase the number of infected animals over 20 years following introduction of 500 infected animals from a mean of 180 to 240, with the 95th percentile increasing from 400 to 530. The simulation results suggest that the new cases are caused by a higher concentration of the infective agent in animal feed. Potential human exposure increases slightly (from a mean of 3,800 to 4,000 cattle oral ID_{50}s) due to the higher number of infected animals in the U.S. The R_0 parameter is slightly higher than in the base case, but still well below 1 even at the 95th percentile (95th 0.45 in the base case *vs.* 0.52 in this analysis).

Sensitivity 4 – Higher Assumed Beef on Bone Consumption Rates

As expected, the changes embodied in this scenario have little effect on the spread of BSE among cattle. Moreover, predicted potential human exposure increases only modestly from a mean of 3,800 cattle oral ID_{50}s in the base case to 4,500 ID_{50}s in this scenario. The 95th percentile increases from 8,700 to 9,400. Changes in beef on bone consumption have no effect on the R_0 values. Overall, uncertainty in this parameter is not particularly influential, although pessimistic assumptions lead to slightly higher levels of potential human exposure.

Sensitivity 5 – Pessimistic *Antemortem* Inspection BSE Detection Rates

Because *antemortem* inspection is a food safety step, it is not surprising that changing the assumed performance of the *antemortem* inspection process has almost no impact on the predicted number of new BSE cases. The mean increases slightly to 190 new cases, while the 95th percentile increases from 400 animals in the base case to 420 in this scenario. Presumably this increase reflects additional BSE infectivity passing through the slaughter process to rendering, making it available to cattle *via* contamination, mislabeling, or misfeeding. On the other hand, predicted human exposure to BSE-contaminated food does increase noticeably to a mean of 6,600 ID_{50}s over 20 years, compared to 3,800 ID_{50}s in the base case. The mean value of R_0 increases slightly to 0.25 from 0.24, and the 95th percentile value for this parameter remains well below 1.0 at 0.46.

Sensitivity 6 – Longer Incubation Period

Evidence suggests that the incubation period (time from infection to manifestation of disease signs – and maximum infectivity) for TSEs depends on the initial infectivity dose delivered (see for example, (McLean 2000)). While the Harvard BSE model incorporates variable incubation periods (see Section 3.1.1.6 of Cohen *et al.* (2003a)), the length of the incubation period does not depend on the magnitude of the BSE dose causing infection. Evidence from the Attack Rate Study (personal communication, Danny Mathews, Veterinary Laboratory Authority / DEFRA, UK, 2005) suggests that the incubation period is positively associated with dose. A longer incubation period can substantially influence the size of the typical infectivity load that is recycled. If the incubation period is sufficiently long, animals will be far more likely to be sent to slaughter or die of other causes before developing clinical signs of disease and the associated high infectivity loads. Results from the 500-animal version of the base suggest that animals dieing late in the incubation cycle play an important role in the simulation outcome. In that scenario, about 40% of the infected animals (260 of 640) die on the farm (*i.e.*, prior to being sent to slaughter). Of these, the vast majority (220 of 260) are rendered, with these animals contributing around 80% of the infectivity that goes into rendering (approximately 1.8 million of 2.2 million cattle oral ID_{50}s).

Investigating the impact of the exposure-dependent incubation period formulation on the simulation results is complicated by the fact that its influence depends strongly on other model assumptions. First, the assumed number of animals among which each feed batch is divided (currently assumed to be 89 animals) influences per animal exposure and hence incubation duration. The results produced by the base case version of the model depend very little on this assumption. For example, cutting in half the number of animals among which each feed batch is divided typically doubles the per-animal exposure risk (unless the infectivity load in the exposure batch is very large), hence preserving the expected number of newly infected animals.

Second, the influence of the exposure-dependent incubation period depends on the assumed exposure among the infected animals introduced at the beginning of the simulation. Because these animals represent nearly three-fourths of the infected animals that die or are sent to slaughter, this exogenous, arbitrary assumption strongly influences the results.

Third, the incubation period would depend on whether the assumed exposure was quantified in terms of susceptibility-adjusted ID_{50}s or unadjusted ID_{50}s. The susceptibility-adjusted ID_{50} exposure estimates take into account the age of the animal. For example, as explained by Cohen *et al.* (2003a), the susceptibility-adjusted exposure for older animals equals the unadjusted exposure multiplied by approximately 0.1. While a rationale has been developed for this adjustment for the purpose of estimating infection probability, it is unknown whether this adjustment should be made for the purpose of estimating the impact on incubation period.

For the purpose of investigating the potential impact of the exposure-dependent incubation period on the simulation results, we used the susceptibility-adjusted exposure level. A review of the simulation's intermediate results indicated that given this assumption, the incubation period for many animals would substantially exceed the median of 4.2 years postulated in the original model (*i.e.*, with exposure-independent incubation periods). To get an idea of how exposure dependence might influence the simulation results (if, for example, we could specify reasonable exposure levels and hence the corresponding incubation periods for the infected animals introduced at the beginning of the simulation), we used the exposure-independent version of the model, doubling the value of each percentile of the incubation period distribution.

Longer incubation periods lead to fewer predicted new cases of BSE. The mean number of new cases during the 20 years following the introduction of 500 infected cattle dropped from 180 to 43, with the 95^{th} percentile dropping from 400 to 130. Potential human exposure to the BSE agent decreased from an average of 3,800 to 1,900 cattle oral ID_{50}s. The decrease in human exposure was proportionally less than the decrease in new BSE cases because human exposure depends on the total number of infected animals (including animals introduced at the beginning of the simulation), rather than on the number of newly infected cases only. Although the number of newly infected animals decreased by approximately 75% (from 180 to 43), the total number of infected animals decreases by only 20% (from 680 to 543). The R_0 parameter decreased significantly to a mean of 0.075 compared to 0.24 in the base case. Even the 95^{th} percentile (0.20) is below the mean of the base case value of 0.24.

Sensitivity 7 and Sensitivity 8

These two scenarios were developed to evaluate the importance of 1) the assumed proportion of cattle showing no clinical signs of disease that are non-ambulatory (Sensitivity 7), and 2) the assumed proportion of clinical animals that are non-ambulatory (Sensitivity 8). The results indicate the assumed proportions are unimportant. Note that Cohen et al. (Cohen 2003a) reported that the assumed performance of the *antemortem* inspection does not substantially influence the predicted number of additional BSE cases in the U.S. or potential human exposure. It is therefore not surprising that parameters influencing ante-mortem detection rates likewise have little influence on the simulation results. Because satisfactory data are not available to estimate the proportion of animals that are non-ambulatory, it is fortunate that better information to quantify these assumptions is not critical for the purpose of using the model.

4 Conclusion

This evaluation has used the simulation model developed by the Harvard Center for Risk Analysis (HCRA)(Cohen 2003a; Cohen 2003b) to analyze the effects of implemented or proposed risk management strategies for reducing the risk of the spread of BSE and potential human exposure to BSE infectivity. We modeled the response of the U.S. agricultural system for 20 years following the import of BSE-infected cattle. Key predictions made by the HCRA simulation model include the number of additional new BSE cases that develop subsequent to this hypothetical introduction, the amount of BSE infective agent in human food and potentially available for human consumption (measured as cattle oral ID_{50}s), and the epidemic's basic reproduction rate, R_0.

Our updated "base case" represents the circumstances in the U.S. prior to the December 2003 discovery of the animal with BSE in Washington state. The model predicts that introduction of BSE would lead to minimal spread of the disease, with an R_0 well below one. Potential human exposure to BSE infectivity is also low.

Our analysis estimated the impact of risk management measures adopted by USDA, considered by FDA, or proposed by the International Review Subcommittee. The model predicts that the food safety measures enacted by USDA all reduce potential human exposure to BSE infectivity to some extent but that a specified risk material ban has a dramatic effect. Removing

non-ambulatory ("downer") cattle from the human food supply reduces predicted potential human exposure by about 3%. Removing high risk tissues, often called specified risk materials or SRMs, from animals over 30 months of age reduces potential human exposure by more than 99% on average. Prohibiting the use of advanced meat recovery (AMR) in the processing of animals over 30 months of age reduces potential human exposure of about 45%. It is worth noting that these measures reduce what is already a small exposure in absolute terms.

We evaluated two FDA proposals, including a prohibition on the use of ruminant blood in ruminant feed, and the requirement that plants producing both prohibited material (*i.e.*, ruminant-derived material) and non-prohibited material use dedicated production lines. Our analysis indicated that neither of these actions would have much impact on the spread of BSE. Our earlier reports (Cohen 2003a) have suggested that blood contributes relatively little to the spread of BSE. Similarly, our earlier work has suggested that cross-contamination of MBM and feed production lines is a relatively minor factor in the spread of BSE.

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. Our evaluation suggests that this measure would reduce potential human exposure by more than 99% and the number of new cases by 80% relative to the base case. This performance reflects our assumption that the ban would cover dead stock and that compliance would be perfect. We estimate that another suggestion made by the International Review Subcommittee, the prohibition of all meat and bone meal in ruminant feed, would decrease the number of new BSE by approximately 5% over 20 years. The remaining cases result primarily from the misfeeding to cattle of rations containing ruminant proteins (feed intended for other species). This measure has virtually no predicted impact on potential human exposure.

Our sensitivity analysis identified the rate of misfeeding (*i.e.*, the deliberate or accidental administration to cattle of feed designated for other species and containing ruminant protein) as an important parameter. If the misfeeding rate is as high as the pessimistic assumption in our sensitivity analysis, the expected number of new BSE cases over 20 years is almost 15 times higher than in the base case and the average value of R_0 is 0.89 (compared to 0.24 in the base case). But the information about plausible misfeeding rates remains uncertain. More information on possible misfeeding rates would increase confidence in our predictions for the potential spread of BSE. The other parameters evaluated as part of the sensitivity analysis (mislabeling and

contamination rates, render reduction factors, beef on bone consumption rates, and the success of *antemortem* inspection at detecting clinically ill BSE cattle) were far less influential.

Finally, if the low prevalence of BSE in the U.S. means cattle are likely to be subject to much smaller exposures to BSE infectivity than in the UK, and if smaller exposures lead to longer BSE incubation periods, as has been suggested some recent evidence, then our sensitivity analysis (analysis number 6) suggests that introduction of BSE might lead to an even smaller number of new BSE cases and less potential human BSE exposure than predicted in our base case. More definitive evaluation of this hypothesis depends on developing a more firm basis for several key assumptions.

References

Anderson, R. M. and May, R. M. (1991). *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press.

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

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

Cohen, J. T., Duggar, K., Gray, G. M., Kreindel, S., Gubara, H., HabteMariam, T., Oryang, D. and Tameru, B. (2003b). A simulation model for evaluating the potential for spread of bovine spongiform encephalopathy to animals or to people. *Prions and Mad Cow Disease*. B. Nunnally and I. Krull. New York, Marcel Dekker, Inc.

Cohen, J. T. and Gray, G. M. (2004). *Comments on USDA Bovine Spongiform Encephalopathy (BSE) Surveillance Plan. Memo to Ron DeHaven, Deputy Administrator, Veterinary Services, APHIS*. Boston, MA, Harvard Center for Risk Analysis.

European Commission (2004). *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.

European Food Safety Authority (2004). 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* **41**: 1-4.

Gray, G. M. and Cohen, J. T. (2004). *Response to Comments Submitted in Response to USDA's Proposed Rule on Importing Beef and Beef Products from Canada*. Boston, MA, Harvard Center for Risk Analysis.

Jaynes, E. T. (1976). Confidence intervals vs. Bayesian intervals. *Foundations of Probability Theory, Statistical Inference, and Statistical Theories of Science. As cited at http://www.causascientia.org/math_stat/ProportionCI.html*. W. L. Harper and C. A. Hooker. Dordrecht, Holland, D. Reidel Publishing Company.

McLean, A. R. and Bostock, C. J. (2000). Scrapie infections initiated at varying doses: an analysis of 117 titration experiments. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* **355**(1400): 1043-1050.

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

U.S. Food and Drug Administration (2003). *Update on Ruminant Feed (BSE) Enforcement Activities (September 30, 2003)*. Center for Veterinary Medicine. Available at: http://www.fda.gov/cvm/index/updates/BSEInspec03.htm.

Wells, G. A. H., Spiropoulos, J., Hawkins, S. A. C. and Ryder, S. J. (2005). Pathogenesis of experimental bovine spongiform encephalopathy: preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle. *Veterinary Record* **156**: 401-407.

Appendix 1 Base Case Parameter File Changes From Earlier Analysis

Appendix 2 Detailed Simulation Output

Appendix 3 Numerical Stability of Simulation Output

Appendix 4 Revisions and Responses to Peer Review Comments