**Table 3-12**
**Annual Number of CWD-Infected Animals Harvested**

| Species | Disease Prevalence[a] | Population Size[b] | Annual Harvest Rate[b] | Infected Animals Harvested per Year[c] |
|---|---|---|---|---|
| Mule deer | 4.9% | $2 \times 10^6$ | 20-25% | 24,500 |
| White tail deer | 2.1% | $3.2 \times 10^7$ | 25% | 168,000 |
| Rocky Mountain Elk | 0.5% | $1.0 \times 10^6$ | 15-20% | 1,000 |
| **Total** | | | | 194,000 |

*Notes:*

a *Refers to the estimated prevalence of CWD among animals harvested from the CWD endemic areas of north central Colorado and southeastern Wyoming (Miller 2000).*

b. *Source (Rocky Mountain Elk Foundation 1997); Lloyd Floyd, personal communication; Quality Deer Management Association's.*

c *Computed using the upper bound annual harvest rate in the fourth column from the left*

*Number of cervid $ID_{50}$s per case*: Because the prevalence rate has been estimated on the basis of post mortem evaluation of brain tissue, they may reflect only those animals that have advanced disease. We assume that there are 10,000 cervid oral $ID_{50}$s per case of disease.

*Fraction of animals rendered*: Only a small portion of cervids harvested for human consumption are likely to be rendered at all. Those that are rendered are most often processed by an independent facility that handles only prohibited rendered material (Franco 2001). We assume that 10% of the harvested cervids are rendered.

*The species barrier*: As noted in Section 2.3.4, the species barrier for the transmission of CWD from cervids to cattle appears to be between $10^5$ and $10^{12}$. We conservatively assume that the species barrier value is $10^5$.

*Proportion of infectivity surviving rendering and administered to cattle*: As described in Section 3.3.3, under present-day conditions (*i.e.*, with the adoption of the feed ban), total cattle population exposure to infectivity is approximately 0.1% as great as the amount of infectivity in animals sent to rendering.

*Total Cattle Population Exposure*: Under present-day conditions, total exposure to CWD is estimated to amount to no more than 2 cattle oral $ID_{50}$s per year, or approximately 0.2 cattle oral $ID_{50}$s per month. As noted above, this estimates reflects several assumptions that are potentially very conservative. The true level of exposure is perhaps much lower.

### 3.3.5 Chronic Wasting Disease: Lateral Transmission

Because the potential impact of this source is insignificant (see Section 2.3.5), we do not quantitatively model its impact on the prevalence of BSE in the U.S. cattle population or its contribution to contamination of the U.S. food supply.

### 3.3.6 Mink

As is the case with cervids, FDA regulations prohibit the administration to cattle of feed fortified with protein derived from mink, although this ban may not completely prevent such exposures. This section describes our development of an upper bound estimate on this exposure, which we estimate to be on the order of 1 cattle oral $ID_{50}$ annually. The true value is likely to be substantially lower, and could be zero. Our methodology is similar to that used to evaluate the exposure risk associated with CWD. Annual cattle exposure to TME attributable to consumption of mink-derived protein is the product of the 1) number of diseased animals harvested, 2) the number of mink $ID_{50}$s per animal slaughtered, 3) the fraction of animals rendered, 4) the inverse of the species barrier, and 5) the proportion of infectivity surviving rendering and administered to cattle.

*Number of diseased animals harvested*: A total of 2.6 million mink are harvested in the U.S. annually (U.S. Department of Agriculture 2001b). The prevalence of disease is unknown. We assume that the prevalence of clinical and pre-clinical disease are both similar to the corresponding rates for scrapie, or approximately 0.1% and 10%, respectively. Hence, we estimate that there are 2,600 clinical animals and 260,000 pre-clinical animals slaughtered each year.

*Number of mink $ID_{50}$s per case*: As we estimated for scrapie, we assume that pre-clinical animals harbor an average of 600 mink $ID_{50}$s, whereas clinical animals harbor 10,000 mink $ID_{50}$s.

*Fraction of animals rendered*: We estimate that 60% of slaughtered mink are rendered (Platt 2001).

*The species barrier*: Experimental transmission of TME from the Stetsonville outbreak to cattle via i.c. inoculation resulted in animals developing a fatal spongiform encephalopathy (Marsh 1991), although it appeared to be distinct from BSE. As with CWD, we assume that the species barrier for TME transmitted to cattle is $10^5$.

*Proportion of infectivity surviving rendering and administered to cattle*: As in the case of CWD, we assume that this value is now 0.1%.

*Total infectivity reaching cattle*: Total infectivity reaching cattle from clinical TME cases amounts to 0.2 cattle oral $ID_{50}$s annually, while the corresponding value for pre-clinical animals is 0.9 cattle oral $ID_{50}$s. The total amounts to 1 cattle oral $ID_{50}$ per year, or approximately 0.1 cattle oral $ID_{50}$s per month. Because this source exposes cattle to substantially less infectivity than does scrapie (as modeled in Section 3.3.3), we do not quantitatively model its impact on the prevalence of BSE in the U.S. cattle population or its contribution to contamination of the U.S. food supply.

### 3.3.7 Pigs

Because the potential impact of this source is insignificant (see Section 2.3.7), we do not quantitatively model its impact on the prevalence of BSE in the U.S. cattle population or its contribution to contamination of the U.S. food supply.

### 3.3.8 Poultry

Because the potential impact of this source is insignificant (see Section 2.3.8), we do not quantitatively model its impact on the prevalence of BSE in the U.S. cattle population or its contribution to contamination of the U.S. food supply.

### 3.3.9 Recycled Waste

Because the potential impact of this source is insignificant (see Section 2.3.9), we do not quantitatively model its impact on the prevalence of BSE in the U.S. cattle population or its contribution to contamination of the U.S. food supply.

## 3.4 Alternative Scenarios Evaluated Using the Simulation Model

The alternative scenarios evaluated using the simulation model fall into three categories. First, we evaluate the plausibility of the model's output by comparing the predicted number of clinical BSE cases to the observed number of clinical BSE cases between 1985 and 2000 in Switzerland (Section 3.4.1). Second, we evaluate the potential for two sources of infectivity (spontaneous disease and cattle imported from the UK during the 1980s) to have introduced BSE into the U.S. prior to the implementation of regulations meant to limit its spread (Sections 3.4.2 and 3.4.3). Finally, we evaluated the extent to which additional risk management actions (implementation of a UK-style specified risk material (SRM) ban, or a ban on the rendering of cattle that die on the farm) reduce the potential spread of BSE among cattle and potential human exposure (Sections 3.4.4 and 3.4.5). Section 4 in Appendix 2 to this report details the parameter file changes made for each of these scenarios.

### 3.4.1 Switzerland

Because there has never been a controlled experiment to quantify the impact of introducing BSE into a country, a true validation of the simulation model described in this report is not possible. Instead, this section describes an evaluation of the model's plausibility that involves modeling the small BSE outbreak observed in Switzerland following the introduction of BSE infectivity from the UK. Working with experts in Switzerland, we identified appropriate parameter values in order to characterize the herd population dynamics, conditions, practices, and procedures in that country. The Switzerland scenario reflects changing conditions over time. In addition to specifying conditions at the beginning of the simulation (1986), the scenario also reflects changes to these conditions in 1990, 1993, 1996, 1998, and 2001.

This scenario, referred to as "Swiss Best Guess", reflects our best estimate of conditions in Switzerland during the period simulated. After describing this scenario, we outline two modifications ("Swiss Alternative 1" and "Swiss Alternative 2") that were developed after comparing the results of Swiss Scenario to empirical data. Swiss Alternative 1 and Alternative 2 were developed to see whether modest changes to our initial assumptions (modifications that are well within the range of plausibility given our underlying uncertainty) could yield results that are more consistent with these empirical findings.

Swiss Best Guess

*1986:* The Switzerland scenario begins in 1986, the year we assume that 67 newly infected Swiss female dairy cattle were incubating BSE (Doherr 1999). Thirty of these cattle are assumed to be 25 months of age and the remaining 37 are assumed to be 26 months of age.

At the same time, the Switzerland scenario assumes that feed containing 4,000 cattle oral $ID_{50}$s was imported. This assumption is based on information that three tons of MBM were imported from the UK between 1985 and 1989. We assume that during that period, MBM from Britain was contaminated with BSE. In particular, we assume that the three tons of MBM imported from Britain represented rendered protein from three cattle, each of which harbored between 800 and 2,000 cattle oral $ID_{50}$s. We assume that the three tons of MBM were used to supplement feed at a concentration of 5% and was therefore distributed as part of a total of 60 tons of feed. Assuming that cattle consume 30 pounds of feed a day (3% of their weight) and that farms purchase feed in lots sufficient to last them 30 days, the 60 tons (120,000 pounds) of feed would be divided among 133 cattle (*i.e.*, 120,000 pounds ÷ (30 pounds/cow-day × 30 days)).

Differences between the base case and the Switzerland scenario in 1986 include the following. First, the misfeeding rate is assumed to be 15%, considerably higher than the 1.6% misfeeding rate in the base case. The assumption of a substantially higher misfeeding rate is based on the observation that a substantial proportion of the farms in Switzerland raise both livestock that can consume prohibited feed and livestock that are restricted to non-prohibited feed. For example, farm census data suggest that nearly 67% of the poultry in Switzerland are raised on farms that also raise cattle (Heim 2001). For hogs, the corresponding proportion is 59% (Heim 2001).

Second, the Switzerland scenario assumes that most rendering systems in use in 1986 in Switzerland used batch processing technology, which normally reduces infectivity by a factor of 1,000 (*i.e.*, 3 logs). However, because use in Switzerland typically did not conform to the 133°C/20 minutes/3 bars of pressure minimum treatment standard, we assume that the majority of rendering facilities achieved only 2 logs of infectivity inactivation.

Finally, the Switzerland scenario reflects the absence of a feed ban in 1986.

*1990:* In December, 1990, Switzerland enacted a feed ban and a ban on the rendering or use as human food of SRM, including brain, spinal cord, dorsal root ganglia, gut, lung, eyes, and AMR meat[5]. The structure of the MBM and feed production industries made failures of the ban on the use of SRM in animal feed more likely. In particular, a substantial portion of the prohibited feed was produced by mixed feed producers. We assume that these producers mislabeled or failed to properly label 10% of their prohibited feed and that contamination occurred during production of 20% of the prohibited feed. We also note that increased efforts to keep specified risk materials (SRM) out of the human supply may have increased pressure to divert the flow of this material into MBM and ultimately into animal feed.

*1993*: By 1993, rendering practices improved. We assume that at that time, all renderers complied with the 133°C/20 minutes/3 bars of pressure standard, and hence that all rendering achieved a 3.1 logs of infectivity reduction (a factor of approximately 1,260).

*1996*: Changes in farming practices also helped reduce the spread of BSE infectivity. These changes included reduced misfeeding of prohibited rations to cattle (we assume this rate was 0.1%) and eliminating the rendering of cattle that had died on the farm.

*1998*: In 1998, slaughter facility practices further improved with an increased effort to remove spinal cords after splitting. We assume the spinal cord was removed 99.9% of the time.

*2001*: Finally, in January, 2001, Switzerland outlawed the practice of feeding MBM to <u>any</u> farm animal[6]. This move essentially eliminated the possibility of misfeeding animals. In addition, Switzerland prohibited the feeding of blood meal to cattle.

<u>Swiss Alternative 1</u>

This scenario is the same as the Swiss Best Guess scenario except that we divided the assumed import of 4,000 cattle oral $ID_{50}$s equally over three months at the beginning of the

[5] The November, 2001 version of this report assumed that this change occurred in January, 1990, rather than in December of that year. We revised this assumption in response to information from the Swiss Federal Veterinary Service Swiss Federal Veterinary Service (2002). Memo (March 18) to the Harvard Center for Risk Analysis: "Comments on the Harvard study: Evaluation of the potential for Bovine Spongiform Encephalopathy in the United States"..

[6] The November, 2001 version of this report assumed that this change occurred in January, 1999. We revised this assumption in response to information from the Swiss Federal Veterinary Service Ibid..

simulation period (1,333 $ID_{50}$s per month) rather than assuming that it was all imported in the same month. Doing so substantially increases the number of initial infections that occur at the beginning of the simulation because the original simulation assumed that these 4,000 $ID_{50}$s were imported in a single month and divided among 133 cattle. Because the size of the exposed group was relatively small for that quantity of infectivity, virtually all the animals received more than 2.0 susceptibility-adjusted $ID_{50}$s, hence "wasting" infectivity. By dividing the delivery over three months, a total of 399 animals were exposed, hence resulting in a greater number of initial infections.

Swiss Alternative 2

This scenario is the same as the Swiss Best Guess Scenario except that a total of 8,000 $ID_{50}$s were introduced into cattle feed in 1986 (rather than 4,000), with the import of this infectivity uniformly distributed over a period of 6 months (1,333 $ID_{50}$s per month).

### 3.4.2 Spontaneous Disease as a Potential Source of Infectivity in the U.S.

This scenario is the same as the spontaneous disease scenario described in Section 3.3.1 except that it also assumes the absence of the 1997 feed ban. We assume that prior to the adoption of the 1997 feed ban, 65% of the MBM produced by renderers that processed cattle went to animal feed manufacturers, while the remaining 35% was either exported or otherwise allocated to some other use that posed no risk of exposing cattle to BSE infectivity. We further assume that 98% of the feed produced by feed manufacturers was sent to farms and that only 2% was allocated to uses that posed no exposure risk to cattle.

### 3.4.3 Cattle Imported into the U.S. from the UK During the 1980s

This scenario evaluates the potential consequences of U.S. imports of cattle from the UK during the 1980s prior to the imposition of an import ban in 1989. Of particular concern has been the import 334 cattle from the UK and 162 cattle from the Republic of Ireland during that period because those animals may have been infected with BSE. The vast majority of the cattle imported from Ireland were regarded as posing a negligible risk because they were imported before 1985 and hence before the prevalence of BSE rose sharply in the UK (Section 3.1.1 in (European Union Scientific Steering Committee 2000d)). Of the animals imported from UK, USDA has determined that 161 were disposed of in a manner that eliminates the possibility that they could have either contaminated the human food supply or lead to the exposure of additional animals in the U.S. to BSE. However, USDA has not been able to conclusively determine that the other 173 animals posed no risk of contaminating either human food or animal feed. This scenario characterizes the potential impact these cattle may have had on the presence of BSE in the U.S.

For each of the 173 animals that may have posed an exposure risk, USDA has determined from Department records and from interviews year of birth, animal type (beef or dairy), gender, age when exported to the U.S., and age when last seen. Using this information, we have computed the probability that the animal was infected and the distribution of values for the animal's total infectivity load. Probabilistically summing these distributions over all 173 cattle yielded a distribution of $ID_{50}$s imported into the U.S. For this scenario, we assume that all infectivity was imported in 1980. Appendix 5 describes our methodology for developing the imported infectivity distribution.

To determine the impact of these imports, we simulated the introduction of various amounts of infectivity in cattle feed into the U.S. Amounts simulated were 0.1, 1.0, 5.0, 10.0, and 50.0 cattle oral $ID_{50}$s. The simulation started in the year 1980 and ran through the year 2010. The following assumptions were made for each time period over that 30-year duration.

*1980*: We assume that at the beginning of the simulation, there was no feed ban in place. In addition, we assume that for cattle between the ages of 12 and 23 months, mis-splits occurred with 5% probability, AMR was used 20% of the time, and spinal cords were removed with 50% probability (regardless of AMR usage). The same assumptions apply to animals 24 months of age and older, except for the mis-split probability, which is assumed to have been 8%. The fraction of spinal cord and DRG that contaminate AMR meat also differs somewhat from the baseline assumptions (see Appendix 2 for details). Finally, we assume that air-injected pneumatic stunning was used for 15% of all animals.

*1993*: We assume that in 1993, the proportion of animals processed in plants using AMR increased from 20% to 40%.

*1997*: The simulation reflects implementation of the feed ban in 1997. However, we assume that at this time, the mislabeling rate for prohibited and mixed renderers was 10% (instead of the base case value of 5%). We also assume that the contamination rate for mixed renderers was 28% (instead of the base case value of 14%). For prohibited and mixed feed producers, we assume that the mislabeling rate was 10% (instead of the base case value of 5%). The probability of contamination for mixed feed producers is assumed to have been 32% (instead of the base case value of 16%).

*1999*: We assume conditions returned to those characterized by the base case assumptions.

### 3.4.4 Risk Management: Specified Risk Materials (SRM) Ban

The SRM ban eliminates the potential for the following tissues to contaminate either human food or rendered material that might be used in feed: brain, spinal cord, gut, eyes, and AMR meat products. The SRM ban also eliminates the practice of rendering animals that die on the farm.

### 3.4.5 Risk Management: A Ban on Rendering Animals that Die on the Farm

Animals that die on the farm are not rendered. We assume that any infectivity in these animals will not contaminate either human food or rendered material that may be used as animal feed.

# 4 Results

This section highlights key results of the analyses in this report. Complete results can be found in Appendices 3A and 3B. Appendix 3C describes how we have summarized the results generated by the simulation using tables and figures.

Section 4.1 discusses the modeled impact of importing ten BSE-infected animals into the U.S. under present-day conditions (*i.e.,* the base case as described in Section 3.1). The model predicts that such an introduction would be unlikely to result in more than a handful of new cases of BSE, that little infectivity would be likely to reach the U.S. human food supply, and that BSE would likely be cleared from U.S. in less than 20 years.

Section 4.2 describes the results of the sensitivity analysès outlined in Section 3.2. In particular, we describe how altering these assumptions influenced the predicted number of new BSE cases and the amount of infectivity potentially available for human consumption following introduction of ten infected animals. The sensitivity analysis results indicate that the predicted number of additional cattle infected is particularly sensitive to the assumed proportion of prohibited MBM that is mislabeled and the assumed proportion of properly labeled prohibited feed that is incorrectly fed to cattle. Predicted human exposure is likewise sensitive to these parameters. It is also sensitive to the assumed number of $ID_{50}$s in the carcass of an animal with full blown BSE, and to a lesser extent to several parameters related to the slaughter process.

The results indicate that both the spread of BSE and potential human exposure are proportional to the number of infected cattle introduced into the U.S. We also investigate the impact of importing contaminated feed.

Section 4.3 describes the predicted impact of different sources of infectivity and evaluates both their plausibility and potential for BSE infectivity to spread to cattle or to be available for potential human exposure. The simulation model predicts that under current conditions (i.e., base case assumptions) cross species transmission of scrapie or spontaneous BSE, if they can occur, would produce one to two new cases of BSE per year in the U.S. and little infectivity to humans. Simulations investigating scenarios in which different numbers of infected cattle are imported into the U.S. indicate that both the spread of the disease among cattle and potential human exposure are roughly proportional to the number of infected animals imported.

In all cases tested (up to 500 infected animals imported), the prevalence of BSE decreases over time and tends to be eventually eliminated from the U.S.

Finally, Section 4.4 describes the model's predictions for the scenarios outlined in Section 3.4. The predictions made by the model for the Switzerland scenario are sufficiently similar to those observed to lend the model credibility. Our analysis of potential imports of BSE-infected animals from the UK into the U.S. during the 1980s shows that it is unlikely although not impossible that these imports introduced BSE into the U.S. cattle population. Finally, the simulation's predictions suggest that two risk management measures (a specified risk material ban or a ban on the rendering of cattle that die on the farm) would each further improve defenses against the spread of BSE in this country.

Section 4.5 concludes our report with a summary of the main findings and the implications of BSE for both animal and public health in the U.S.

Before proceeding, we note that many of the simulation results are "right skewed," meaning that the average value often exceeds the median ($50^{th}$) percentile and can sometimes even exceed the $95^{th}$ percentile. A right-skewed distribution arises when the lower end of the distribution is bounded (in our case, all of the quantities must be non-negative), and rare events can cause very large outcome values. For example, the probability that the brain of a BSE-infected animal will be selected for potential human consumption is very low because there are few sick animals and few brains harvested for human consumption. However, if this event does occur, it makes a substantial quantity of infectivity available for potential human consumption. If this event occurs only five times in 5,000 simulation runs, the arithmetic mean for the number of cattle oral $ID_{50}$s available for human consumption from brain would exceed this outcome's value for 4995 of the 5,000 runs (*i.e.,* zero). For this reason, we report key percentile values for each outcome, in addition to the arithmetic mean. Appendix 3C further describes how we have reported the simulation results. The results discussion focuses on mean and median values to characterize the central tendency for each quantity, and the $95^{th}$ percentile to characterize a quantity's extreme (although not worst possible) case value.

## 4.1 Base Case

The assumptions that define the base case correspond to contemporary conditions in the U.S., including all risk management actions taken by government and industry. Appendix 1, Section 2 details the corresponding parameter values. Because BSE has not been found in the U.S., the base case is evaluated by assuming the import of ten BSE-infected animals. Such an introduction is considered unlikely because of the ban on importing ruminants from countries known to have BSE. However, this approach allows characterization of the way in which infectivity could spread to animals or humans should the disease be introduced.

The introduction of ten infected animals demonstrates the robustness of U.S. regulations and practices against the establishment of BSE (full results can be found in Section 1 of Appendices 3A and 3B). On average, there are fewer than five new cases of BSE, with a 75% chance that there will be no more than one new case, and at least a 50% chance that there will be no new cases at all. The extreme case (the $95^{th}$ percentile of the distribution) predicts 16 new cases. The simulation predicts an average of 39 cattle oral $ID_{50}$s potentially available for human consumption during the 20-year period following the import of the infected animals, with a $95^{th}$ percentile value of 180 cattle oral $ID_{50}$s. In all cases, the disease is quickly eliminated from the U.S., with virtually no chance that there are any infected animals 20 years following the import of infected animals.

Potential human exposure routes include consumption of brain (24% of the total on average), contaminated AMR product (51%), beef on bone (12%), intestine (2 %), and spinal cord (10%). Even these estimates are likely to overstate true human exposure because they represent the amount of infectivity *presented* for human consumption but do not take into account waste or actual consumption rates. For example, the reported quantity for potential exposure of $ID_{50}$s in beef on bone potential reflects the presence of spinal cord and dorsal root ganglia in a fraction of cuts like T-bone steaks. The spinal cord may never be consumed but is still available for potential human exposure. Likewise, not all bovine brain removed for human consumption is actually eaten by humans. Some is not purchased at the retail level and some is not consumed even when purchased. These issues are also relevant to the other tissue categories. For these reasons, our estimates of potential human exposure are likely to overestimate true exposure to infected BSE tissues.

To further characterize the resilience of the U.S. agriculture system, we simulated the impact of introducing 1, 5, 20, 50, 100, 200 or 500 infected cattle (see Section 4.3.3).

## 4.2 Sensitivity Analyses

This section describes how the use of worst case assumptions in the scenario hypothesizing the introduction of ten infected cattle into the U.S. influences the findings detailed in Section 4.1.

As described below, we find that with three exceptions, the model continues to predict with a high level of certainty that the U.S. agricultural system remains robust against the spread of disease unless worst case values are assigned to multiple parameters simultaneously. In particular, the model's predictions change most dramatically if parameters in the feed production, MBM production, and feed administration practices parameter group are simultaneously assigned worst case values. Because the worst case values are unlikely to be correct for multiple parameters simultaneously, the sensitivity analysis suggests that the findings from Section 4.1 are reasonable. Nonetheless, it would be helpful to develop better information for those parameters that do contribute most substantially to the uncertainty of our findings.

Appendix 3A, Section 2 summarizes the results for each scenario (one table per set of assumptions evaluated). Appendix 3D summarizes the results for each quantity across all scenarios. The results in Section 3D clearly illustrate our finding that most alternative sets of assumption have virtually no impact on the simulation results. Moreover, simultaneously assigning worst case values to both the cattle demographic assumptions and the MBM production, feed production, and feeding practice assumptions has a far greater impact than any other alternative evaluated.

### 4.2.1 Number of Additional Infected Cattle

As noted in the introduction of Section 3.2, using the base case assumptions results in an $R_0$ value that is virtually certain to be less than unity, indicating that the prevalence of BSE would decrease over time after being introduced into the U.S. Figure 4-1 illustrates how each alternative worst case assumption individually influences the predicted number of additional new cases of BSE over a 20-year period after the introduction of ten infected animals.

Figure 4-1 can be interpreted by considering an approximate correspondence between the number of additional infected cattle and the value of $R_0$. Roughly speaking, if $R_0$ is unity (*i.e.*, each infected animal infects one additional animal), we would expect the number of additional infected animals to be the product of the number of infection cycles and the number of initial animals infected. The infection cycle is the duration between the infection of an animal and that animal's death, at which point the cycle can initiate the next round of infections. The longest this period can be is the length of the incubation period plus the amount of time the animal remains clinical before dying. The average incubation duration is 52 months, while the average time the animal remains clinical is four months. Hence, the average incubation cycle is 56 months long. As a result, there are approximately four full infection cycles per 20 year period, indicating that if $R_0$ is unity, there should be approximately 40 additional infected animals following the introduction of ten initial infected animals.

We note that this estimate is likely to be conservative because the true infection cycle duration is likely to be less than the average incubation period. For example, in the base case, more than half the infected animals died at slaughter (8.3), rather than on the farm (6.0). The 8.3 animals that died at slaughter produced 1,600 $ID_{50}$s, far less than would be expected if the animals had survived through the entire incubation period. Hence, an $R_0$ equal to unity should probably result in more than 40 additional infected animals. Nonetheless, we will use the value of 40 additional animals for the purpose of evaluating the sensitivity analysis findings.

The results illustrated in Figure 4-1 indicate that with the exception of three parameters (3.2..3.1 – Render reduction factor, 3.2.3.5 – Render mislabeling, and 3.2.3.6 – Misfeeding), use of worst case assumptions in place of base case assumptions produces $R_0$ values that remain below unity with at least 95% probability. Even for these last three parameters, use of worst case values results in $R_0$ values exceeding unity with less than 25% probability. For example, for the worst case assumptions for misfeeding, the number of additional infected cattle has a 50$^{th}$ percentile value of 1 ($R_0 < 1$), and a 75$^{th}$ percentile value of 16 ($R_0 < 1$). Only the 95$^{th}$ percentile, which is 420, implies an $R_0$ value exceeding unity. (The mean value is 64). The results also show that with the exception of the render reduction factor paramter, the render mislabeling parameter, and the misfeeding parameter, none of the worst case assumptions substantially change the results distribution, when compared to the base case (first distribution on left side of Figure 4-1).

Figure 4-2 illustrates the impact of assigning worst case values to multiple parameters simultaneously. In this figure, worst case values were assigned simultaneously to all demographic parameters (Section 3.2.1), all slaughter process parameters (Section 3.2.2), and all MBM production, feed production, and feed administration parameters (Section 3.2.3). Assigning worst case values to all demographic parameters has a modest impact on the number of additional infected cattle. The 75th percentile value is 1 ($R_0$ <1). At the 95th percentile, the number of additional infected cattle (48) slightly exceeds the cutoff we have estimated as corresponding to an $R_0$ of 1. Setting all slaughter process parameters to their worst case value has a similar modest impact on the number of additional infected cattle. Again, only the 95th percentile (43 additional infected cattle) corresponds to an $R_0$ value exceeding 1. Because the feed and MBM parameters include the three parameters that had the greatest univariate impact on the number of additional infected cattle (see Figure 4-1), it is not surprising that assigning worst case values to all the parameters in this set has a substantially greater impact on the number of additional infected cattle. Assigning worst case values to all of these parameters simultaneously results in an $R_0$ value exceeding unity at the 75th percentile.

The three rightmost box and whisker plots in Figure 4-2 illustrate the impact of assigning worst case values to two groups of parameters simultaneously. Assigning worst case values to the demographic parameters and to the slaughter process parameters simultaneously (Sections 3.2.1 and 3.2.2) has only a modest impact on the predicted number of infected cattle. Simultaneously assigning worst case values to the slaughter process and MBM production, feed production, and feed practice parameters (Sections 3.2.2 and 3.2.3) has a somewhat more pronounced impact. The largest impact results when worst case values are simultaneously assigned to all the demographic parameters and to the MBM production, feed production, and feed practice parameters (Section 3.2.1 and 3.2.3). The predicted BSE spread that results is so large that the run time required to simulate this scenario made it impractical to generate 5,000 iterations. Instead, the results reflect a total of 780 iterations. As the detailed results indicate (see Section 2.5.5 in Appendix 3A), with these assumptions the spread of BSE is consistent with an $R_0$ value that exceeds unity with between 25% and 50% probability. Moreover, the degree to which $R_0$ can exceed unity in these cases is substantial.

We did not simulate the scenario in which all parameters are simultaneously assigned their worst-case values for three reasons. First, the results described in the preceding paramgraph indicate that assigning worst case values to two of the three sets of parameters (demographic assumptions and MBM production, feed production, and feed practice parameters) is sufficient to change the predicted behavior of the agricultural system. Second, the extended run time (250 hours on a 3 GHz Windows-compatible PC) needed to generate 780 iterations for this scenario makes testing an even more extreme scenario appear to impractical. Finally, the probability that the worst case values are valid for all parameters seems to be remote.

### 4.2.2 Infectivity in Food Available for Human Consumption

Figures 4-3 and 4-4 illustrate the results for the univariate and multivariate sensitivity analyses conducted for the estimated number of $ID_{50}$s in food available for human consumption. Figure 4-3 shows that, as with the number of new infected cattle (Section 4.2.1), use of a worst case assumption for any individual parameter has in most cases a limited impact on potential human exposure to BSE-contaminated food. The only exceptions appear to be two of the influential parameters identified in Section 4.1 (3.2.3.5 – Render mislabeling, and 3.2.3.6 – Misfeeding) and the assumed number of $ID_{50}$s in the carcass of a full-blown BSE case (3.2.2.1a – $ID_{50}$s in carcass). In any case, total human exposure over the 20-year period of the simulation remains limited no matter which parameter is assigned its worst case value. Even when the most influential parameter (3.2.3.6 – misfeeding) is assigned its worst case value, the $95^{th}$ percentile exposure is 1,000 $ID_{50}$s over 20 years. Lower percentile values were substantially less, with a $75^{th}$ percentile of 110 $ID_{50}$s and a median of 21 $ID_{50}$s.

Figure 4-4 illustrates the impact of assigning worst case values to groups of parameters simultaneously. The results indicate that the demographic parameters (3.2.1) have a limited impact on potential human exposure to BSE-contaminated food, but that collectively, both the slaughter process parameters (3.2.2) and the feed and MBM parameters (3.2.3) have a more substantial impact. Interestingly, although the combination of the slaughter process group parameters and feed and MBM parameters (3.2.2 and 3.2.3) increase the $5^{th}$, $25^{th}$, $50^{th}$, and $75^{th}$ percentiles to the greatest extent (compared to the base case results), the combination of the demographic parameters and feed and MBM parameters (3.2.1 and 3.2.3) increase the $95^{th}$ percentile, and consequently the arithmetic mean, to the greatest extent.

## 4.3 Alternative Sources of Infectivity

We evaluate three potential sources of BSE in the U.S. Section 4.3.1 considers the impact of assuming BSE can develop spontaneously in cattle with an incidence rate that mirrors the age-specific incidence of CJD in humans. Section 4.3.2 considers the import of various numbers of infected cattle (1, 5, 20, 50, 200, and 500) and the import of contaminated feed (10,000 $ID_{50}$s). Finally, Section 4.3.3 considers the impact of assuming that scrapie can be transmitted from sheep to cattle. In all of these cases we assume the conditions specified in the base case hold.

### 4.3.1 Spontaneous BSE

For this scenario, the model predicts an average of 27 infected animals over a 20-year period ($95^{th}$ percentile value of 38). It is predicted that only 2.7 animals, on average, would reach the clinical stage of the disease ($95^{th}$ percentile of 6). Virtually all animals that become infected develop the disease spontaneously, although maternal transmission and transmission caused by contaminated protein both make a small contribution. The simulation predicts that a mean of 73 cattle oral $ID_{50}$s would be potentially available for human consumption ($95^{th}$ percentile value of 220).

These results suggest that if this hypothesis is true, the disease is essentially endemic, with one-to-two cases occurring each year. Current agricultural practices and regulations (the feed ban) effectively check the spread of disease to other cattle but the disease cannot be eliminated because of its sporadic occurrence. The very low number of animals developing clinical signs would make detection using any method of surveillance very difficult.

### 4.3.2 Imports

Figures 4-5, 4-6, and 4-7 respectively illustrate the relationship between the number of infected cattle imported and the number of new cases (*i.e.,* the number of cases in addition to the imported animals) during the 20 year period following the arrival in the U.S. of these imports, potential human exposure to BSE during this period, and the probability that BSE will be present in the U.S. at the end of the 20-year period. In Figures 4-5 and 4-6, the medians are connected by a solid line. The results indicate that all three outcomes increase linearly as a function of the number of infected cattle introduced. Most importantly, Figure 4-7 shows that even after the introduction of 500 cattle, the probability that BSE is still present in the U.S. after 20 years has dropped to approximately 10%. This finding suggests that the prevalence of BSE decreases over time regardless of how large the introduction is. That is, the value of $R_0$ remains less than one.

We note also that following the introduction of contaminated feed containing 10,000 $ID_{50}$s, the median simulation predictions are: a total of 1,600 cattle infected over 20 years, potential human exposure to approximately 4,300 cattle oral $ID_{50}$s, and that after 20 years, an 18% chance that BSE still remains in the U.S. By comparing these results to the median predictions in Figures 4-5 and 4-6, and the probability predictions in Figure 4-7, we can characterize the impact of importing contaminated feed in terms of the number of infected cattle that would have the same impact. Assuming the linear relationships in these figures hold at higher levels, the import of 10,000 $ID_{50}$s has the same impact on the spread of BSE (newly infected cattle) as importing 3,600 infected cattle. It has the same impact on human exposure as importing 1,100 infected cattle. Finally, it has the same impact on the persistence of the disease (*i.e.*, probability that it is present in the U.S. after 20 years) as the import of 820 infected cattle.

### 4.3.3 Scrapie

This simulation evaluates the impact of assuming that scrapie contributes one cattle oral $ID_{50}$ to feed consumed by cattle each month. The simulation predicts that this contamination results in an average of 38 infected cattle over a period of 20 years ($95^{th}$ percentile estimate of 64). The simulation also predicts that an average of about six animals would develop clinical signs during that period ($95^{th}$ percentile of 12). Current surveillance would be unlikely to detect this number of clinical cases. On average, the simulation predicts that approximately 100 cattle oral $ID_{50}$s would be available for potential human exposure during the 20 y ear period ($95^{th}$ percentile estimate of 290).

Because scrapie is assumed to contaminate cattle feed continually, the disease would essentially be endemic. Note that the simulation predicts that most new cases of BSE would arise directly from exposure to scrapie infectivity, although a small number of cases would result from exposure to contaminated ruminant protein that slips through the feed ban. Maternal transmission also makes a small contribution to the total.

We expect that the predictions made here are likely to overstate the true contribution of scrapie to BSE, as explained in Section 3.3.3. In brief, it is likely that the true species barrier is greater than the value of 1,000 used (efforts to transmit North American scrapie orally to cattle have produced negative results in all instances), and the prevalence of scrapie in the U.S. is probably less than the UK prevalence rates used in the calculation. Section 3.3 of Appendices 3A and 3B detail the simulation results.

## 4.4 Alternative Scenarios

This section details the results of several simulations designed to investigate further factors influencing spread of BSE infectivity. The first scenario described models the small BSE outbreak in Switzerland to evaluate the plausibility of our model (section 4.4.1). Next we examine the spontaneous hypothesis by looking at how spontaneous disease might have spread in the years before the FDA feed ban was adopted (section 4.4.2). Section 4.4.3 examines how the import of cattle from the UK during the 1980s may have affected the U.S. The last two sections evaluate specific risk management strategies, including a specified risk material (SRM) ban identical to that imposed in the UK (Section 4.4.4), and a prohibition on the rendering of animals that die on the farm (Section 4.4.5).

### 4.4.1 Switzerland

As discussed in Section 3.4.1, our model is not amenable to formal validation because there have been no controlled experiments in which the consequences of BSE introduction into a country have been monitored and measured. However, as a test of the model's plausibility, we modeled the small BSE outbreak reported in Switzerland following the introduction of BSE infectivity from the UK. Our simulation took into account risk management actions taken by the Swiss during the ensuing period (*e.g.,* the introduction of a feed ban regulation).

The model predicts both the total number of infected animals in Switzerland and the incremental number that develop clinical signs of disease. Only animals with clinical signs could be detected using the standard surveillance methods available early in the outbreak (although current surveillance practices can detect disease in animals several months before development of clinical signs). We therefore compare the monthly clinical case incidence predicted by the model to the empirical clinical case incidence estimates reported by Doherr *et al.* (1999). As illustrated in Figure 4-8, the modeled incidence rate increases above zero around two years before the empirical rate, peaks at about one-half the empirical rate, and declines to zero at around the same time the empirical rate declines to zero. The modeled cumulative incidence is approximately 60% the empirical cumulative incidence. If empirical counts reflect underreporting, the actual incidence of clinical cases may exceed the modeled incidence by an even greater degree than the approximate factor of two suggested by Figure 4-8. Doherr *et al.* raise the possibility of underreporting by as much as 75%. However, Doherr *et al.* suggest that these substantial underreporting rates most likely apply to "*cases late in incubation or with early clinical signs*" (p. 159). It is therefore plausible that the overall underreporting rate for clinical cases would be much lower.

Even without an adjustment for potential underreporting, the modeled estimates described above understate the empirically reported case incidence rate. However, as described in Section 3.4.1, these modeled values reflect an initial best-guess set of assumptions with no adjustments made to try to match the empirical counts. Our results indicate that only modest changes to the assumptions (Swiss Alternative 1 and Swiss Alternative 2) are needed to achieve such a congruence. Given the level of uncertainty associated with the scenario-specific assumptions, the results in Figure 4-9 indicate that the Alternative 1 assumptions produce results that come reasonably close to matching the empirical counts. The Alternative 2 assumptions produce results that come reasonably close to matching twice the empirical counts. Complete simulation results appear in Section 4.1 of Appendices 3A and 3B.

Our model's modest underprediction of clinical cases could be due to incorrect specification of the number of infected animals imported or the amount of contaminated feed introduced, among other factors. At the same time, the similarity of our predictions and the observations from Switzerland provide some confidence that the model's structure and approach are reasonable. It is important to note that this is not a true validation and, in fact, the model's predictions could be close to reported observations for the "wrong reasons." However, given the absence of data suitable for validating the model, the results of the Switzerland scenario are encouraging.

### 4.4.2 Spontaneous With no Feed Ban

To further investigate the spontaneous hypothesis, we modeled a scenario in which spontaneous disease occurs using the rates described in Section 3.3.1, but no feed ban is present to mitigate the recycling of infectivity in ruminant feed. The scenario, described in Section 3.4.2 was run for 20 years.

The absence of a feed ban allows BSE infectivity to rapidly spread throughout the cattle population. The mean projection for this scenario suggests 42,000 animals infected over the 20 year period (95th percentile of 190,000). The average number of clinical animals predicted is 1,500 (95th percentile of 6,600).

It should be noted that the simulation often predicts that the BSE prevalence rapidly increases towards the end of the twenty year period (see Section 4.2 in Appendices 3A and 3B for complete results). This tendency suggests that if a longer time period were simulated, the model would predict a much greater burden of disease. Hence, while some simulation runs predict prevalence rates that are low enough to be compatible with the fact that BSE has not been detected in the U.S., the results suggests that even in these cases, the prevalence would climb much higher if a longer period were simulated. That is, in the absence of a feed ban, the prevalence would most likely reach a detectable level in any case in just over 20 years. The fact that BSE was not detected in the U.S. prior to the implementation of the feed ban therefore suggests that either spontaneous disease either does not occur, or that its incidence is less than we have assumed. Alternately, the imposition of the feed ban may have stopped an epidemic before it could reach detectable levels. In that case, the base case results suggest that the feed ban will eliminate the disease shortly.

### 4.4.3 Cattle Imported from the UK in the 1980s

This scenario investigates the likelihood that BSE infectivity could have been introduced into the U.S. by the import of 173 cattle from the UK during the 1980s that may have contaminated either human food or animal feed (see Section 3.4.3). We also determine the amount of infectivity that may have been introduced. Using these findings, we characterize the likelihood that BSE could have been introduced into the U.S. and remained undetected.

As discussed in Section 3.4.3, some of the cattle imported into the U.S. from the UK between 1980 and 1989 may have been infected with BSE without showing clinical signs of the disease. As a result, diseased animals may have contaminated animal feed in this country. Figure 4-10 illustrates the cumulative distribution for the amount of infectivity (cattle oral $ID_{50}$s) that may have been in feed consumed by cattle in the U.S. (see methodology in Section 3.4.3 and in Appendix 5). The distribution indicates it is likely (probability of 82%) that U.S. cattle were exposed to no infectivity from cattle imported from the UK. The probability that cattle were exposed to no more than 0.1 $ID_{50}$s is 84%, the probability that they were exposed to no more than one $ID_{50}$ is 86%, the probability that they were exposed to no more than five $ID_{50}$s is 91%, the probability that they were exposed to no more than ten $ID_{50}$s is 93%, and the probability that they were exposed to no more than 50 $ID_{50}$s is 96%.

To characterize the impact of introducing infectivity into the U.S. during the 1980s, we have simulated the introduction of 0.1, 1.0, 5.0, 10.0, and 50.0 cattle oral $ID_{50}$s into cattle feed in 1980, and followed the evolution of the U.S. cattle population through 2010. The results of these simulations (see Section 4.3 in Appendices 3A and 3B) can be used to quantify the likely number of clinical BSE cases that would have occurred and hence to assess the plausibility of these scenarios in light of the fact that BSE has not been detected in the U.S. In particular, introductions that result in too large a number of clinical cases to be compatible with the fact that BSE has not been detected in the U.S. are not plausible.

Note that the distributions for the output quantities are highly skewed, indicating that under most circumstances the infectivity did not spread widely but that occasionally, there was a combination of events leading to significant numbers of infected cattle. For example, when 0.1 cattle oral $ID_{50}$ is introduced into feed, more than 4,750 of the 5,000 simulation runs for this scenario produced no new cases of disease. However, a few runs produced substantial numbers of diseased animals. Hence the mean number of infected animals (over all 5,000 simulations) is 45, and the mean number of animals with clinical signs is ten. Introducing larger quantities of infectivity also yields right-skewed results distributions.

The probability that BSE was introduced into the U.S. depends on two events – the introduction of contaminated material from imported animals into domestic cattle feed (probability of 18%), and the infection of exposed cattle and the subsequent spread of BSE to other animals without the creation of so many cases that it would have been likely to have been discovered by surveillance. Figure 4-11 illustrates for the year 2000 (year 20 of the simulation) the predicted number of cattle with clinical signs following the introduction of 0.1, 1.0, 5.0, 10.0, or 50.0 cattle oral $ID_{50}$s from the imported UK animals into feed administered to U.S. cattle in 1980. Also plotted is the USDA's estimate of the number of clinical cases surveillance would have detected in the year 2000 with 95% probability based on the methods and level of surveillance at the time (Bridges 2001; U.S. Department of Agriculture 2002). For example, the curve in Figure 4-11 corresponding to the introduction of 10.0 $ID_{50}$s indicates that there is an 82%

chance that this introduction caused no new BSE cases in the U.S.[7], and that it could have resulted in a maximum of approximately 1,100 clinical cases in the year 2000. However, all values exceeding the detection limit of 470 clinical cases in the year 2000 (*i.e.*, above the horizontal "detection limit" line) are implausible because no BSE has been detected in the U.S. For the introduction of 10.0 $ID_{50}$s, there is a 6% chance that the number of clinical cases in 2000 would have exceeded this limit (*i.e.*, a 94% chance that this value would have been below the detection limit). Hence, even if cattle in the U.S. did consume 10.0 $ID_{50}$s in 1980, there is only a 12% chance (94% minus 82%) that it resulted in BSE cases that have not been found. Corresponding probabilities can be computed for the other $ID_{50}$ introductions considered.

Taken together, Figures 4-10 and 4-11 are useful for evaluating the likelihood that BSE cattle imports from the UK during the 1980s introduced BSE into the U.S. but resulted in too few cases for the disease to have been detected. First, there is only an 18% chance that cattle in the U.S. were exposed to any infectivity (see Figure 4-10). Second, if cattle were exposed to infectivity, there is only a limited probability that both 1) any cattle in the U.S. became infected, and 2) the number of clinical cases (in the year 2000) was less than the number that would have been likely to have been detected (see Figure 4-11).

Finally, the Figures in Section 4.3 of Appendix 3B illustrate how the disease spreads and contracts if it is introduced into the U.S. The figures suggest that the number of animals with detectable disease peaks in year 20 of the simulation (calendar year 2000) and declines thereafter. This prediction indicates that even if infectivity has been introduced from UK cattle imported before 1989, the disease rate has peaked and BSE will eventually be eradicated. The decline in the predicted disease prevalence in the U.S. is due primarily to the introduction of the FDA feed ban in 1997.

### 4.4.4 Specified Risk Material Ban

Many countries with BSE have prohibited the use of certain tissues in either animal feed or human food. These specified risk material (SRM) bans focus on tissues carrying the greatest

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[7] Figure 4-9 illustrates the number of clinical cases in the year 2000, not the total number of BSE cases caused by the import of BSE-infected cattle from the UK. However, the scenario simulated assumes that action to mitigate the spread of BSE in the U.S. occurs only after implementation of the feed ban in 1997. Hence, as suggested by the figures in Section 4.3 of Appendix 3B, the number of clinical animals peaks

amount of BSE infectivity. To evaluate how such a ban would influence the spread of BSE in the U.S., we altered the base case scenario as described in section 3.4.4 to mimic the UK SRM ban.

The SRM ban has a dramatic effect on both potential human exposure and the spread of BSE among cattle. Following the introduction of 10 infected cattle, as in the base case, the mean number of new BSE cases is reduced by nearly 90% (from 4.3 to 0.53) and the mean number of cattle oral $ID_{50}$s potentially available for human exposure decreases by 95% (from 39 to 1.8). Results for this scenario appear in Section 4.4 of Appendices 3A and 3B.

### 4.4.5 Prohibition on Rendering Animals that Die on the Farm

The results for the base case simulation (section 4.1 and Section 1 in Appendices 3A and 3B) clearly indicate that if BSE is introduced into the U.S., the greatest potential source feed contamination is animals that die prior to being sent to slaughter (animals that die on the farm) and are rendered. The simulations in this report assume that an animal lives for between two and six months following the development of clinical signs. Rendering an animal that has reached the clinical stage of disease introduces the maximum amount of infectivity into rendering and potentially into feed. Hence, a single breach of the feed ban can introduce expose cattle to a substantial amount of BSE infectivity.

The simulation results indicate that banning the rendering of animals that die on the farm would substantially reduce the spread of BSE to other cattle following introduction of ten infected cattle. Compared to the base case, the mean number of new cases decreases by more than 80% (from 4.3 to 0.77). Although this approach targets the spread of BSE to other animals, it also influences potential human exposure to BSE infectivity, decreasing this quantity by more than 20% because it decreases the number of new BSE cases. Complete results appear in Section 4.5 of Appendices 3A and 3B.

## 4.5 Summary

This report addresses the potential for BSE to become a major animal health problem or substantially contaminate the human food supply in the U.S. The results characterize the

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around the year 2000. As a result, if there are zero clinical animals in the year 2000, it is almost certain that few if any animals were infected in the U.S.

robustness of regulations and practices in the U.S., and help to identify data or research that would most increase confidence in our predictions. In addition, the results help to characterize the potential impact that various sources of BSE may have had in the U.S. in the past, including cattle imported from the UK in the 1980s. Finally, the simulation can be used to characterize the effectiveness of additional risk management strategies.

We recognize that the identification of a single case of BSE in the U.S. would have important ramifications for public opinion, trade, and other areas. Yet this analysis demonstrates that even if BSE were somehow to arise in the U.S., few additional animals would become infected, little infectivity would be available for potential human exposure, and the disease would be eradicated. In short, the U.S. appears very resistant to a BSE challenge, primarily because of the FDA feed ban, which greatly reduces the chance that an infected animal would infect other animals. However, the effectiveness of the feed ban is somewhat uncertain because compliance rates are not precisely known.

Potential sources of human exposure to BSE infectivity can be divided into two categories: specific high-risk tissues and contamination of low-risk tissues. Although not widely popular in the U.S., both brain and spinal cord are consumed by some members of the population. If BSE were present in the U.S., these tissues would be an obvious source of exposure. Our analysis indicates that the most important means by which low risk tissue can become contaminated is the use of advanced meat recovery (AMR) technology, which can leave spinal cord or dorsal root ganglia (DRG) in the recovered meat. Our analysis further indicates that mis-splitting of the spinal column and the resulting incomplete removal of the spinal cord is largely responsible for contamination of AMR meat. In addition, we assume that even in the absence of mis-splitting, some amount of DRG is extracted whenever vertabrae are processed by AMR. Contamination due to aerosolization of the spinal cord during splitting contributes substantially less contamination even though it occurs every time an infected animal is processed.

Despite the potential for the consumption of high risk-tissues and the contamination of low-risk tissues, our results indicate that only small amounts of infectivity are available for human consumption. The import of one infected animal yields an average of 3.7 cattle oral $ID_{50}$s for potential human exposure over a 20 year period, while the import of ten infected cattle results in an average of 39 cattle oral $ID_{50}$s this period. These results can be put into context by comparing them to potential human exposure in the UK where it is estimated almost one million cattle were infected over a 15 to 20 year period. If the UK population was potentially exposed to only one cattle oral $ID_{50}$ from each of these animals, potential human exposure in the UK would dwarf our projections for the U.S. At this time, just over 100 cases of variant Creutzfeldt-Jakob disease (the human TSE linked to BSE) have been identified in the UK, although projections range from a few hundred to tens of thousands of eventual cases. If cattle oral $ID_{50}$s available for human consumption is a good indicator of possible disease risk, it is unlikely the UK experience would be duplicated in the U.S.

There are a number of model assumptions that cannot be verified with confidence, some of which substantially influence the conclusions drawn. With regard to estimating the spread of BSE among cattle, the most influential sources of uncertainty are related to compliance with the FDA feed ban. Within this category, the most important source of uncertainty is the misfeeding rate on farms. Misfeeding prohibited feed (containing ruminant protein) to cattle on farms that raise both cattle and either pigs or chickens completely compromises the feed ban. This practice is the focus of efforts to understand how animals born after the implementation of feed bans in Europe have become infected with BSE. Uncertainty with respect to compliance rates can be reduced with field work and data collection. A second source of uncertainty associated with the feed ban is the proportion of feed produced that is mislabeled (*i.e.*, lacks the proper labels identifying it as feed not to be administered to ruminants). Finally, assumptions regarding the prevalence of alternative rendering technologies used (and hence the degree to which rendering may reduce the level of infectivity in tissue processed to produce MBM) also influence the predicted spread of BSE.

Improving estimates of compliance with the feed ban would also improve the precision of our estimates of potential human exposure to BSE-contaminated meat. The assumed number of $ID_{50}$s per clinical case of BSE also has a notable impact on predicted potential human exposure to BSE.

We have identified three important ways in which BSE could be introduced into the U.S: 1) cross-species transmission from a native TSE like sheep scrapie, 2) spontaneous development of the disease in native animals, or 3) the import of an infected animal or animal product from a country with BSE. The analysis suggests that either cross-species transmission of a TSE (scrapie) or spontaneous disease, if they can occur, would cause only a few cases of BSE each year and would result in relatively little potential human exposure. However, results from our evaluation of the impact of spontaneous BSE on the U.S. prior to the 1997 FDA feed ban casts doubt on the plausibility of this potential source of BSE. In particular, our results suggest there is a substantial probability that the number of animals with clinical signs would be sufficiently high to be inconsistent with the fact that surveillance has failed to detect BSE in the U.S. At the same time, the simulation results indicate that there is a non-trivial probability that spontaneous BSE would generate an insufficient number of animals to be detected by surveillance.

Although it is not possible to know if an infected animal was imported from the UK in the 1980s, our analysis suggests it is highly unlikely. First, the imported animals whose disposition is not known came from farms where the disease was not found in any animal born during the same year. Second, the beef breeding animals imported had little exposure to potentially infected protein supplements while in the UK. Finally, many of the animals are known to have lived beyond the average incubation period once they arrived in the US. Nonetheless, there is some small probability that at least one of these animals was infected and that infectivity from such an animal contaminated feed consumed by cattle in the U.S. Exposure to infectivity among U.S. cattle could not have been substantial because in the years prior to the 1997 FDA feed ban, such exposure would have eventually resulted in a substantial number of clinical cases, a prediction that is inconsistent with the fact that BSE has not been identified in the U.S. to date. There is therefore a small chance that BSE could have been introduced into the U.S. and remained undetected. Even if BSE was introduced, actions by USDA and FDA have already arrested the spread of the disease and have begun to reduce its prevalence. If BSE is present in the U.S., these actions will ultimately lead to the disease's eradication.

Evaluation of potential risk management actions highlights an additional benefit of this type of analysis. The insights provided by the model demonstrate that interventions very early in the rendering and feed production process can avoid the need for other, more obvious, measures. Specifically, removing most of the infectivity from rendered product can protect human and animal health even if the feed ban is not 100% effective. Both disposing of all specified risk materials and prohibiting the rendering of animals that die prior to being sent to slaughter, *i.e.,* animals that may have died of BSE and hence have high levels of infectivity, reduce potential new cases of BSE by more than 80%. The misfeeding rate, a key parameter identified in our sensitivity analysis, is not important if the infectivity in prohibited MBM is greatly reduced or eliminated. The SRM ban also reduces substantially the amount of infectivity available for potential human exposure. Of course, it must be recognized that even in the absence of these measures, animal health risks and human exposure are both small, with the import of ten infected cattle leading to an average of fewer than five new cases of BSE and potential human exposure to 39 cattle oral $ID_{50}$s.

As we strive to learn more about BSE and limit the extent of the disease, the model developed for this analysis has many potential uses. It is flexible and can be changed easily. For example, if appropriate data are available, its parameters can be modified so that other countries or regions can be simulated. Specific scenarios of interest can be evaluated, including risk management actions under consideration. The model can also be used to evaluate hypotheses about sources and factors influencing the BSE's spread. We hope this model will find a place among the useful tools for understanding and controlling BSE.

# Glossary

**AMR (Advanced Meat Recovery)** – FSIS (U.S. Department of Agriculture (FSIS) 2002) states that "*AMR systems remove the attached skeletal muscle and edible tissues from carcasses without breaking or crushing bones. This machinery separates meat by scraping, shaving or pressing the muscle and edible tissue away from the bone. However, unlike traditional mechanical separation, AMR machinery cannot break, grind, crush or pulverize bones to separate muscle tissue. Bones must emerge essentially intact and in natural physical conformation.*"

**APHIS (Animal Plant Health Inspection Services)** – APHIS is an agency that is part of the U.S. Department of Agriculture.

**BSE (Bovine Spongiform Encephalopathy)** – BSE is a slowly progressive and fatal prion disease of adult cattle. The disease is characterized for spongy changes in the brain and a long incubation period.

**BSE Inquiry** - Inquiry established by the UK Prime Minister to investigate the emergence and identification of Bovine Spongiform Encephalopathy (BSE) and variant Creutzfeldt Jakob Disease (vCJD) as well as the government response. The Inquiry was established on March 20, 1996.

**Bypass protein** – Bypass protein is the feed protein that escapes digestion in the rumen and passes into the lower digestive tract where is digested and absorbed. Bypass proteins are important proteins in the nutrition of dairy animals.

**CJD (Creutzfeldt-Jakob Disease)** – CJD is a fatal prion disease that has been known for many years to affect human. It can be transmitted as the result of consuming contaminated tissue (as part of canabilistic rituals) or when contaminated tissue is used in surgical procedures.

**CNS (Central Nervous System)** – The CNS consists of nervous tissue that includes brain and spinal cord.

**Codon** – A series of 3 successive nucleotides in nucleic acid that specifies a particular amino acid or signal sequence in a protein.

**CWD (Chronic Wasting Disease)** – CWD is a prion disease that affects white tail deer, mule deer and elk. The disease has been found only in North America.

**Distal Ileum** – The distal ileum is the lower portion of the small intestine.

**Downer Cattle** – See "non-ambulatory cattle."

**DRG (Dorsal Root Ganglia)** – DRG are the nervous tissue that are located within the bones of the vertebral column. DRG contain nerve cells that transfer sensory signals from parts of the body to the spinal cord.

**FDA** – U.S. Food and Drug Administration

**FFI (Fatal Familial Insomnia)** – FFI is a rare human familial prion disease.

**FSE (Feline Spongiform Encephalopathy)** – FSE is a prion disease that affects cats. Exposure to the BSE agent is the most likely explanation for the emergence of the disease.
**FSIS (Food Safety and Inspection Service)** – FSIS is an agency that is part of the U.S. Department of Agriculture.

**Genotype** – Genetic constitution of an individual organism. In particular, this term refers to the specific chromosomal alleles that determine specific traits.

**GSS (Gerstmann-Sträussler-Scheinker)** – GSS is a rare familial prion disease that affects humans.

**HCRA** – Harvard Center for Risk Analysis.

**Heterozygous** – This term refers to organisms that have two different alleles of the same gene.

**Histopathology** – The study of microscopic changes in diseased tissues.

**Homozygous** – This term refers to individuals that have two identical alleles of the same gene.

**Horizontal transmission** – Transmission within a population other than by genetic or maternal means.

**i.c. (intracerebral) inoculation** – Injection into the brain

**$ID_{50}$ (Infectious Dose 50)** – An $ID_{50}$ is the amount of infectious material (e.g., infective bovine brain) that when consumed results in disease infection with 50% probability. The amount of material that constitutes one $ID_{50}$ depends on the route of exposure (*e.g.*, oral administration or intracerebral inoculation).

**Immune response** – This response is the action taken by the body to minimize the damage resulting from the presence of a foreign agent in the body.

**Immunohistochemistry** – Techniques for staining cells or tissues using labeled antibodies against specific proteins.

**Incubation period** – The period between infection and clinical manifestation of the disease.

**Infectivity** – Infectivity is a general term referring to the agent that is capable of passing on disease.

**i.p. (intraperitonal) inoculation** – Injection into the abdominal cavity.

**Kuru** – Kuru is a rare human prion disease found in the Fore population of Papua, New Guinea.

**Mad-Cow Disease** – The colloquial name for bovine spongiform encephalopathy.

**MAFF (The UK Ministry of Agriculture, Fisheries and Food)** – MAFF has been renamed the Department of Environment Food and Rural Affairs (DEFRA).

**Maternal Transmission** – Transmission from dam to offspring *in utero* (during pregnancy) or during the intermediate post partum period

**MBM (Meat-and-bone meal)** – MBM is a dried homogenized material produced by rendering animal tissues. MBM is used as a protein source in the production of animal feed.

**MRM (Mechanically Recovered Meat)** – MRM is defined as "*...residual material, off bones, obtained by machines operating on auger, hydraulic or other pressure principles in such a manner that the cellular structure of the material is broken down sufficiently for it to flow in puree form from the bone*" (BSE Inquiry 2000b).

**Non-ambulatory cattle** – Non-ambulatory cattle include animals that are unable to rise. This condition is common and usually affects animals around parturition. It can also result from a variety of causes, including neurological disease.

**Non Prohibited Feed** – Non-prohibited feed does not contain proteins derived from ruminants and/or mink and can therefore be legally administered to ruminants.

**Non Prohibited MBM** – Non-prohibited meat and bone meal does not contain proteins derived from ruminants and/or mink and hence can legally be used in the preparation of ruminant feed.

**OIE (Office International des Epizooties)** – OIE determines animal health standards for international trade, advises the veterinary services in member countries and aims to work towards the eradication of the most dangerous animal and zoonotic diseases. As of May, 2003, 164 countries belonged to the OIE.

**Pathogenesis** – This term refers to the process by which disease develops in an organism.

**Pre-clinical** – Refers to the disease stage prior to the manifestation of clinical signs or symptoms.

**Prion Disease** – Prion diseases are a family of fatal brain diseases that occur in a number of mammals including humans. These diseases are also known as Transmissible Spongiform Encephalopathies (TSE's). Prion diseases are caused by the build-up of abnormal proteins in the central nervous system.

**Prohibited Feed** – Prohibited feed contains ruminant protein or mink protein and therefore cannot be legally used to produce feed for ruminants.

**Prohibited MBM** – Prohibited meat and bone meal contains ruminant protein or mink protein and therefore cannot be legally used to produce feed for ruminants.

**PrP (Prion Proteins)** – Prions are proteins that occur naturally in animals and humans. Research suggests that if a prion is folded incorrectly and hence has an abnormal shape, it can induce disease. Moreover, when mis-shaped proteins come into contact with normal proteins, they can "recruit" the normal proteins, causing them to become mis-shaped. Some scientists believe that if this process progesses sufficiently, prions can damage the brain, causing it to become spongy and filled with holes. This phenomenon gives rise to the scientific name for mad cow disease (bovine spongiform encephalopathy).

**$PrP^{C}$, $PrP^{Sen}$** – The normally folded form of PrP.

**PrPgene** – Gene found in mammals that determines the amino acid sequence for the $PrP^{C}$ protein.

**$PrP^{Sc}$, $PrP^{Res}$** – The abnormally folded disease-specific isoform of PrP.

**Rendering** – Rendering is processing of offal and discarded parts of animal carcasses to produce two products: meat and bone meal (MBM) and tallow. The rendering process consists of drying, cooking, and separating the solid fraction (protein meals) form the melted liquid fraction (tallow).

**Ruminant** – Animal that chews the cud (partially digested food) regurgitated from its rumen, and has a stomach with four compartments.

**Scrapie** – Scrapie is a prion disease that affects sheep and goats.

**SEAC (Spongiform Encephalopathy Advisory Committee)** – Established in UK to advise the government on matters related to TSEs (prion diseases).

**Spinal Cord** – The part of the nervous system that runs through the spine or vertebral column.

**SRM (Specified Risk Material)** – Tissues in in cattle, sheep and goats such as brain tissue and spinal cord, that are most likely to contain the BSE infective agent.

**SSC (Scientific Steering Committee)** – Established in the European Community to advise its members on matters related to TSE's (prion diseases) and other zoonoses.

**Tallow** – The fat produced by the rendering process.

**TME (Transmissible Mink Encephalopathy)** – TME is a prion disease that affects mink. The disease has been found several countries.

**TSEs (Transmissible Spongiform Encephalopathies)** – See prion disease.

**USDA** – United States Department of Agriculture

**vCJD (variant Creutzfeldt-Jakob Disease)** – vCJD is the name of the human prion disease that is thought to be caused by consumption of BSE-contaminated meat.

**Vertebral Column** – The supporting line of bones that make up the spine and house the spinal cord.

**Vertical Transmission** – Transmission of disease from parent to the offspring. See also maternal transmission.

**Western Blot** – A method use for detecting proteins, including diseased PrP. This method can be used to diagnose TSEs.

**WHO** – World Health Organization.

**Zoonosis** - Animal diseases that can be transmitted to humans.

## References:

Agrimi, U., Ru, G., Cardone, F., Pocchiari, M. and Caramelli, M. (1999). Epidemic of transmissible spongiform encephalopathy in sheep and goats in Italy. *Lancet* **353**(9152): 560-1.

Airtime and Resources, I. (2001). Hypotheses for the origin and spread of BSE. *http://sparc.airtime.co.uk/bse/hypoth.htm#15*.

Alpers, M. (1970). Kuru in New Guinea: its changing pattern and etiologic elucidation. *American Journal of Tropical Medicine & Hygiene* **19**(1): 133-7.

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

Anderson, R. M., Donnelly, C. A., Ferguson, N. M., Woolhouse, M. E., Watt, C. J., Udy, H. J., MaWhinney, S., Dunstan, S. P., Southwood, T. R., Wilesmith, J. W., Ryan, J. B., Hoinville, L. J., Hillerton, J. E., Austin, A. R. and Wells, G. A. (1996). Transmission dynamics and epidemiology of BSE in British cattle. *Nature* **382**(6594): 779-788.

Andreoletti, O., Berthon, P., Marc, D., Sarradin, P., Grosclaude, J., van Keulen, L., Schelcher, F., Elsen, J. and Lantier, F. (2000). Early accumulation of PrP(Sc) in gut-associated lymphoid and nervous tissues of susceptible sheep from a Romanov flock with natural scrapie. *Journal of General Virology*. **81**(12): 3115-26.

Anil, M. H., Love, S., Williams, S., Shand, A., McKinstry, J. L., Helps, C. R., Waterman-Pearson, A., Seghatchian, J. and Harbour, D. A. (1999). Potential contamination of beef carcases with brain tissue at slaughter. *Veterinary Record* **145**(16): 460-462.

anonymous (1996). Surveillance for Creutzfeldt-Jakob disease--United States. *MMWR - Morbidity & Mortality Weekly Report* **45**(31): 665-8.

Belt, P., Muileman, I., Schreuder, B. E. C., Ruijter, J. B., Gilkens, A. L. J. and Smits, M. A. (1995). Identification of five allelic variants of sheep PrP gene and their association with natural scrapie. *Journal of General Virology* **76**(509-517).

Biopharm (1997). Assessment of the Risk of Bovine Spongiform Encephalopathy in Pahrmaceutical Products. *http://www.biopharm-mag.com/resources/pharma0198.htm*.

Bolton, D. C., McKinley, M. P. and Prusiner, S. B. (1982). Identification of a protein that purifies with the scrapie prion. *Science* **218**(4579): 1309-11.

Borras, T. and Gibbs, C. J., Jr. (1986). Molecular hybridization studies with scrapie brain nucleic acids. I. Search for specific DNA sequences. *Archives of Virology* **88**(1-2): 67-78.

Bossers, A., Belt, P., Raymond, G. J., Caughey, B., de Vries, R. and Smits, M. A. (1997). Scrapie susceptibility-linked polymorphisms modulate the in vitro conversion of sheep prion protein to protease-resistant forms. *Proceedings of the National Academy of Sciences of the United States of America* **94**(10): 4931-6.

Bradley, R. (1999). BSE transmission studies with particular reference to blood. *Developments in Biological Standardization* **99**: 35-40.

Brewer, R. (2000). U.S. Department of Agriculture, Food Safety and Inspection Service. Personal Communication.

Bridges, V. (2001). U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Centers for Epidemiology & Animal Health. Personal Communication.

Brown, P., Rodgers-Johnson, P., Cathala, F., Gibbs, C. J., Jr. and Gajdusek, D. C. (1984). Creutzfeldt-Jakob disease of long duration: clinicopathological characteristics, transmissibility, and differential diagnosis. *Annals of Neurology* **16**(3): 295-304.

Brown, P., Cervenakova, L., Goldfarb, L. G., Mc Combie, W. R., Rubenstein, R., Will, R. G., Pocchiari, M., Martinez-Lage, J. F., Scalici, C., Masullo, C., Graupera, G., Ligan, J. and Gajdusek, D. C. (1994a). Iatrogenic Creutzfeldt-Jakob disease: An example of the interplay between ancient genes and modern medicine. *Neurology* **44**: 291-293.

Brown, P., Gibbs, C. J., Rodgers-Johnson, P., Asher, D., Sulima, M., Bacote, A., Goldfarb, L. and Gajdusek, D. (1994b). Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Annals of Neurology 35*(5): 513-29.

Brown, P. (1998a). On the origins of BSE. *Lancet* **352**(9124): 252-253.

Brown, P. and Bradley, R. (1998b). 1755 and all that: a historical primer of transmissible spongiform encephalopathy. *BMJ* **317**(7174): 1688-92.

Brown, P., Cervenakova, L., McShane, L. M., Barber, P., Rubenstein, R. and Drohan, W. N. (1999). Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans [see comments]. *Transfusion* **39**(11-12): 1169-78.

Bruce, M. and Fraser, H. (1982). Focal and asymetrical vacuolar lesions in the brains of mice infected with certain strains of scrapie. *Acta Neuropathol* **58**: 133-140.

Bruce, M., McBride, P. and Facquhar, C. (1989). Precise targeting of the pathology of the sialoglycoprotein PrP, and neuronal vacualization in mouse scrapie. *Neurosci. Lett* **102**: 1-6.

Bruce, M., Chree, A., McConnell, I., Foster, J., Pearson, G. and Fraser, H. (1994). Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **343**(1306): 405-11.

Bruce, M. E., McConnell, I., Fraser, H. and Dickinson, A. G. (1991). The disease characteristics of different strains of scrapie in Sinc congenic mouse lines: implications for the nature of the agent and host control of pathogenesis. *Journal of General Virology* **72**(Pt 3): 595-603.

Bruce, M. E., Will, R. G., Ironside, J. W., McConnell, I., Drummond, D., Suttie, A., McCardle, L., Chree, A., Hope, J., Birkett, C., Cousens, S., Fraser, H. and Bostock, C. J. (1997). Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* **389**(6650): 498-501.

BSE Inquiry (2000a). Conclusions drawn from the scientific response to BSE. *http://www.bseinquiry.gov.uk/report/volume1/execsum2.htm* **2: Science**.

BSE Inquiry (2000b). *The Inquiry into BSE and variant CJD in the United Kingdom. Volume 13: Industry Processes and Controls. 4. Mechanically Recovered Meat.* Available at: http://www.bseinquiry.gov.uk/report/volume13/chaptec2.htm.

Bueler, H., Aguzzi, A., Sailer, A., Greiner, R. A., Autenried, P., Aguet, M. and Weissmann, C. (1993). Mice devoid of PrP are resistant to scrapie. *Cell* **73**(7): 1339-47.

Canadian Food Inspection Agency Animal Products Animal Health and Production (2001). Chronic Wasting Disease (CWD) of Deer and Elk. *http://www.inspection.gc.ca/english/anima/heasan/disemala/cwdmdce.shtml.*

Caramelli, M., Ru, G., Casalone, C., Bozzetta, E., Acutis, P., Calella, A. and Forloni, G. (2001). Evidence for the
transmission of scrapie to sheep and goats from a vaccine against Mycoplasma agalactiae. *Veterinary Record* **148**(17): 531-6.

Carlson, G. A., DeArmond, S. J., Torchia, M., Westaway, D. and Prusiner, S. B. (1994). Genetics of prion diseases and prion diversity in mice. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **343**(1306): 363-9.

Cervenakova, L., Goldfarb, L. G., Garruto, R., Lee, H. S., Gajdusek, D. C. and Brown, P. (1998). Phenotype-genotype studies in kuru: implications for new variant Creutzfeldt-Jakob disease. *Proceedings of the National Academy of Sciences of the United States of America* **95**(22): 13239-41.

Chesebro, B. (1999). Prion protein and the transmissible spongiform encephalopathy diseases. *Neuron* **24**(3): 503-6.

CJD Surveillance Unit (2001). Information on the new variant of CJD. *http://www.cjd.ed.ac.uk/.*

Clark, W. W., Hourrigan, J. L. and Hadlow, W. J. (1995). Encephalopathy in cattle experimentally infected with the scrapie agent. *American Journal of Veterinary Research* **56**(5): 606-12.

Collinge, J., Palmer, M. and Dryden, A. (1991). Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* **337**(8755): 1441-2.

Collinge, J., Sidle, K. C., Meads, J., Ironside, J. and Hill, A. F. (1996). Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD [see comments]. *Nature* **383**(6602): 685-90.

Collinge, J. and Palmer, M. (1997). Human Prion Diseases. *Prion Diseases*. J. Collinge and M. Palmer, Oxford University Press: 18-49.

Cullie, J. and Chelle, P. (1936). La maladie dite tremblante du mouton, est-elle inoculable? *Comptes rendu de l' Academie des Sciences* **203**: 1552-1554.

Cullie, J. and Celle, P.-L. (1939). Transmission experimentale de la tremblante chez la chevre. *Comptes Rendus Academie des Sciences* **208**: 1058-1060.

Cutlip, R., Miller, J., Hamir, A., Peters, J., Robinson, M., Jenny, A., Lehmkuhl, H., Taylor, W. and Bisplinghoff, F. (2001). Resistance of cattle to scrapie by the oral route. *Canadian Journal of Veterinary Research.* **65**(2): 131-132.

Cutlip, R. C., Miller, J. M., Race, R. E., Jenny, A. L., Katz, J. B., Lehmkuhl, H. D., DeBey, B. M. and Robinson, M. M. (1994). Intracerebral transmission of scrapie to cattle. *Journal of Infectious Diseases* **169**(4): 814-20.

Cutlip, R. C., Miller, J. M. and Lehmkuhl, H. D. (1997). Second passage of a US scrapie agent in cattle. *Journal of Comparative Pathology* **117**(3): 271-5.

Dawson, M., Wells, G. A. H., Parker, B. N. J. and Scott, A. (1990). Primary, parenteral transmission of BSE to a pig. *Vet. Rec.* **127**: 338.

de Koeijer, A., Schreuder, B., Heesterbeek, H., Oberthur, R., Wilesmith, J. and de Jong, M. (1999). *BSE Risk Assessment by Calculating the Basic Reproduction Ratio for the Infection Among Cattle*. Lelystad, The Netherlands, Institute for Animal Science and Health.

Det Norske Veritas (1997). *Risk from BSE via environmental pathways.*

Detwiler, L. (1992). Scrapie. *Revue Scientifique et Technique* **11**(2): 491-537.

Detwiler, L. (2000). U.S. Department of Agriculture, Animal and Plant Health Inspection Service. Personal Communication.

Detwiler, L. (2001). U.S. Department of Agriculture, Animal and Plant Health Inspection Service. Personal Communication.

Dickinson, A., Fraser, H. and Outram, G. (1976). Scrapie incubation time can exceed natural lifespan. *Nature* **256**(5520): 732-3.

Dickinson, A. G. and Meikle, V. M. (1971). Host-genotype and agent effects in scrapie incubation: change in allelic interaction with different strains of agent. *Molecular & General Genetics* **112**(1): 73-9.

Dickinson, A. G. and Outram, G. W. (1988). Genetic aspects of unconventional virus infections: the basis of the virino hypothesis. *Ciba Foundation Symposium* **135**: 63-83.

Diringer, H., Beekes, M. and Oberdieck, U. (1994). The nature of the scrapie agent: the virus theory. *Annals of the New York Academy of Sciences* **724**: 246-58.

Dlouhy, S. R., Hsiao, K., Farlow, M. R., Foroud, T., Conneally, P. M., Johnson, P., Prusiner, S. B., Hodes, M. E. and Ghetti, B. (1992). Linkage of the Indiana kindred of Gerstmann-

Sträussler-Scheinker disease to the prion protein gene. *Nature Genetics* **1**(1): 64-7.

DNV (Det Norske Veritas) (1997). *Assessment of Risk from possible BSE infectivity in dorsal root ganglia*. Report C7831, Rev 1. London, UK.

Doherr, M. G., Heim, D., Vandevelde, M. and Fatzer, R. (1999). Modelling the expected numbers of preclinical and clinical cases of bovine spongiform encephalopathy in Switzerland. *Veterinary Record* **145**(6): 155-60.

Donnelly, C. (1998). Maternal transmission of BSE: Interpretation of the data on the offspring of BSE-affected pedigree suckler cows. *Veterinary Record* **142**(21): 579-580.

Donnelly, C. and Ferguson, N. (2000). *Statistical Aspects of BSE and vCJD*, Chapman & Hall/CRC.

Donnelly, C. A., Ferguson, N. M., Ghani, A. C., Wilesmith, J. W. and Anderson, R. M. (1997a). Analysis of dam-calf pairs of BSE cases: Confirmation of a maternal risk enhancement. *Proceedings of the Royal Society of London - Series B: Biological Sciences* **264**(1388): 1647-56.

Donnelly, C. A., Ferguson, N. M., Ghani, A. C., Woolhouse, M. E., Watt, C. J. and Anderson, R. M. (1997b). The epidemiology of BSE in cattle herds in Great Britain. I. Epidemiological processes, demography of cattle and approaches to control by culling. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **352**(1355): 781-801.

Duguid, J. R., Rohwer, R. G. and Seed, B. (1988). Isolation of cDNAs of scrapie-modulated RNAs by subtractive hybridization of a cDNA library. *Proceedings of the National Academy of Sciences of the United States of America* **85**(15): 5738-42.

Eastern Research Group, I. (1996). TSE Regulatory Options Cost Analysis. *http://www.fda.gov/cvm/index/bse/tse1.pdf*.

Ebringer, A., Thorpe, C., Pirt, J., Wilson, C., Cunningham, P. and Ettelaie, C. (1997). Bovine spongiform encephalopathy: is it an autoimmune disease due to bacteria showing molecular mimicry with brain antigens? *Environmental Health Perspectives* **105**(11): 1172-4.

Elsen, J. M., Amigues, Y., Schelcher, F., Ducrocq, V., Andreoletti, O., Eychenne, F., Khang, J. V., Poivey, J. P., Lantier, F. and Laplanche, J. L. (1999). Genetic susceptibility and transmission factors in scrapie: detailed analysis of an epidemic in a closed flock of Romanov. *Archives of Virology* **144**(3): 431-45.

European Commission (1999a). The evaluation of tests for the diagnosis of Transmissible Spongiform Encephalopathy in Bovines (8 July 1999). *http://europa.eu.int/comm/food/fs/bse/bse12_en.html*.

European Commission (1999b). No evidence for BSE transmission through milk. *http://europa.eu.int/comm/dgs/health_consumer/library/press/press28_en.html*.

European Commission (2000). Commission Decision of 5 June 2000 amending Decision 98/272/EC on epidemio-surveillance for transmissible spongiform encephalopathies (notified under document number C(2000) 1144).

European Commission (2001). Chronological overview of Community legislation concerning BSE. *http://europa.eu.int/comm/food/fs/bse/bse15_en.pdf.*

European Union Scientific Steering Committee (1998a). Opinion on possible links between BSE and Organophosphates used as pesticides against ecto- and endoparasites in cattle - Report and opinion adopted at the Scientific Steering Committee meeting of 25-26 June 1998.

European Union Scientific Steering Committee (1998b). Opinion on the Safety of Gelatine adopted at the Scientific Steering Committee at its plenary meeting of 26-27 March 1998 following a public consultation on the preliminary opinion adopted on 19-20 February 1998 (Version updated on 3.04.98) - Background. *http://europa.eu.int/comm/food/fs/sc/ssc/out09_en.html.*

European Union Scientific Steering Committee (1999a). *Opinion of the Scientific Steering Committee on the Human Exposure Risk (HER) via food with respect to BSE - Adopted on 10 December 1999.* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out67_en.html.

European Union Scientific Steering Committee (1999b). *Report on The Risk Born by Recycling Animal By-Products as Feed with Regard to Propagating TSE's in Non-ruminant Farmed Animals.* Prepared by a Working Group for the Scientific Steering Committee as an input in the elaboration of the opinion on the same subject adopted on 16-17 September 1999. Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out59_en.html.

European Union Scientific Steering Committee (2000a). *Opinion - Oral Exposure of Humans to the BSE Agent: Infective Dose and Species Barrier Adopted by the SSC at its Meeting of 13-14 April 2000 Following a Public Consultation via Internet Between 6 and 27 March 2000.* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out79_en.pdf.

European Union Scientific Steering Committee (2000b). *Minutes of the Scientific Steering Committee Meeting of 20-21 January 2000* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out72_en.html.

European Union Scientific Steering Committee (2000c). *Opinion of the Scientific Steering Committee on a Method for Assessing the Geographical BSE-Risk (GBR) of a Country or Region (update, January 2000)* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out68_en.pdf.

European Union Scientific Steering Committee (2000d). *Report on the Assessment of the Geographical BSE - Risk of USA (July 2000).* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out137_en.pdf.

European Union Scientific Steering Committee (2000e). *Opinion on the Safety of Ruminant Blood With Respect to TSE Risks Adopted by the SSC at its Meeting of 13-14 April 2000.* Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out74_en.pdf.

Ferguson, N., Donnelly, C., Woolhouse, M. and Anderson, R. (1999). Estimation of the basic reproduction number of BSE: the intensity of transmission in British cattle. *Proceedings of the Royal Society of London - Series B: Biological Sciences.* **266(1414):23-32,**(1414): 23-32.

Ferguson, N. M., Donnelly, C. A., Woolhouse, M. E. and Anderson, R. M. (1997a). A genetic interpretation of heightened risk of BSE in offspring of affected dams. *Proceedings of the Royal Society of London - Series B: Biological Sciences* **264**(1387): 1445-55.

Ferguson, N. M., Donnelly, C. A., Woolhouse, M. E. and Anderson, R. M. (1997b). The epidemiology of BSE in cattle herds in Great Britain. II. Model construction and analysis of transmission dynamics. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **352**(1355): 803-838.

Fitzsimmons, W. M. and Pattison, I. H. (1968). Unsuccesful attempts to transmit scrapie by nematode parasites. *Research in Veterinary Science* **9**: 281-283.

Floyd, L. (2001). Kansas Department of Wildlife and Parks. Personal Communication.

Foster, J., Bruce, M., McConnell, I., Chree, A. and Fraser, H. (1996). Detection of BSE infectivity in brain and spleen of experimentally infected sheep. *Vet Rec.* **138**(22): 546-8.

Foster, J., Parnham, D., Chong, A., Goldmann, W. and N., H. (2001). Clinical signs, histopathology and genetics of
experimental transmission of BSE and natural scrapie to sheep and goats. *Veterinary Record.* **148**(6): 164-71.

Foster, J. D., McKelvey, W. A., Mylne, M. J., Williams, A., Hunter, N., Hope, J. and Fraser, H. (1992). Studies on maternal transmission of scrapie in sheep by embryo transfer. *Veterinary Record* **130**(16): 341-3.

Foster, J. D., Hope, J. and Fraser, H. (1993). Transmission of bovine spongiform encephalopathy to sheep and goats. *Veterinary Record* **133**(14): 339-41.

Franco, D. (2001). Vice President, National Renderers Association. Personal Communication.

Fraser, H. and Dickinson, A. (1968). The sequential development of brain lesions of scrapie in three strains of mice. *J. Comp. Pathol.* **78**: 301-311.

FSIS Directive 7160.2 (1997). "Meat" prepared using advanced mechanical meat/bone separation machinery and meat recovery systems. *http://www.fsis.usda.gov/oppde/rdad/fsisdirectives/fsisdir7160%2D2.pdf*.

Gajdusek, D. C., Gibbs, C. J. and Alpers, M. (1966). Experimental transmission of a Kuru-like syndrome to chimpanzees. *Nature* **209**(25): 794-6.

Gale, P. and Stanfield, G. (2001). Towards a quantitative risk assessment for BSE in sewage sludge. *Journal of Applied Microbiology* **91**(3): 563-569.

Garland, T., Bauer, N. and Bailey, M., Jr. (1996). Brain emboli in the lungs of cattle after stunning [letter] [see comments]. *Lancet* **348**(9027): 610.

Gibbs, C. J., Gajdusek, C. J. and Amyx (1979). Strain variation in the viruses of Creutzfeldt-Jakob disease and kuru. *Slow Transmissible Diseases of the Nervous System.* S. Prusiner and W. Hadlow, Academic Press, New York. **2:** 87-110.

Gibbs, C. J., Jr., Safar, J., Ceroni, M., Di Martino, A., Clark, W. W. and Hourrigan, J. L. (1990). Experimental transmission of scrapie to cattle. *Lancet* **335**(8700): 1275.

Glatzel, M. and Aguzzi, A. (2001). The shifting biology of the prions. *Brain Research Reviews* **In press.**

Goldmann, W., Hunter, N., Martin, T., Dawson, M. and Hope, J. (1991). Different forms of the bovine PrP gene have five or six copies of a short, G-C-rich element within the protein-coding exon. *Journal of General Virology* **72**(Pt 1): 201-4.

Goldmann, W., Hunter, N., Somerville, R. and Hope, J. (1996). Prion phylogeny revisited. *Nature* **382**(6586): 32-3.

Gordon, W. S. (1939). *Studies of louping-ill, tick borne fever and scrapie.* 3rd International Congress for Microbiology.

Gordon, W. S. (1946). Louping ill, tickborne fever and scrapie. *Veterinary Record* **58**: 516-525.

Gordon, W. S. (1959). *Scrapie Panel.* Proceedings of 63rd Annual Meeting of the US LivestockSanitary Association.

Gould, D. (2000). *Geographically Targeted Survey of Cattle in Northeast Colorado for Evidence of Chronic Wasting Disease (CWD).* United States Animal Health Association.

Griebel, P. J. and Hein, W. R. (1996). Expanding the role of Peyer's patches in B-cell ontogeny. *Immunology Today* **17**(1): 30-9.

Hadlow, W., Race, R. and RC, K. (1987). Experimental Infection of sheep and goats with transmissible mink spongiform encephalopathy virus. *Canadian Journal of Veterinary Research* **51**: 135-144.

Hadlow, W. J. (1959). Scrapie and kuru. *Lancet*(ii): 289-290.

Hadlow, W. J., Kennedy, R. C., Race, R. E. and Eklund, C. M. (1980). Virologic and neurohistologic findings in dairy goats affected with natural scrapie. *Veterinary Pathology* **17**(2): 187-99.

Hadlow, W. J., Kennedy, R. C. and Race, R. E. (1982). Natural infection of Suffolk sheep with scrapie virus. *Journal of Infectious Diseases* **146**(5): 657-64.

Hamir, A., Cutlip, R., Miller, J., Williams, E., Stack, M., Miller, M., O'Rourke, K. and Chaplin, M. (2001). Preliminary findings on the experimental transmission of chronic wasting disease agent of mule deer to cattle. *J Vet Diagn Invest.* **13**(1): 91-96.

Hansen, M. (1999). Creutzfeldt-Jakob disease. *New England Journal of Medicine.* **340**(21): 1689.

Harbour, D. (2001). *Measures to reduce contamination of meat and environment with CNS tissue during slaughter and processing of cattle and sheep*. School of Medicine, University of Bristol. Available at: http://europa.eu.int/comm/research/press/1998/pr2710en.html.

Hartsough, G. R. and Burger, D. (1965). Encephalopathy of the mink. I . Epizootiologic and clinical observations. *Journal of Infectious Diseases* **115**: 387-392.

Heim, D. (2001). Swiss Federal Veterinary Office. Personal Communication.

Hill, A. F., Desbruslais, M., Joiner, S., Sidle, K. C., Gowland, I., Collinge, J., Doey, L. J. and Lantos, P. (1997). The same prion strain causes vCJD and BSE. *Nature* **389**(6650): 448-50.

Hill, A. F., Antoniou, M. and Collinge, J. (1999). Protease-resistant prion protein produced in vitro lacks detectable infectivity. *Journal of General Virology* **80**(Pt 1): 11-4.

Hill, A. F., Joiner, S., Linehan, J., Desbruslais, M., Lantos, P. L. and Collinge, J. (2000). Species-barrier-independent prion replication in apparently resistant species. *Proceedings of the National Academy of Sciences of the United States of America* **97**(18): 10248-53.

Hoinville, L., McLean, A. R., Hoek, A., Gravenor, M. B. and Wilesmith, J. (1999). Scrapie occurrence in Great Britain. *Veterinary Record* **145**(14): 405-6.

Hoinville, L. J. (1994). Decline in the incidence of BSE in cattle born after the introduction of the 'Feed Ban'. *Veterinary Record* **134**: 274-275.

Hoinville, L. J. (1996). A review of the epidemiology of scrapie in sheep. *Revue Scientifique et Technique* **15**(3): 827-52.

Holman, R. C., Khan, A. S., Kent, J., Strine, T. W. and Schonberger, L. B. (1995). Epidemiology of Creutzfeldt-Jakob disease in the United States, 1979-1990: analysis of national mortality data. *Neuroepidemiology* **14**(4): 174-81.

Horn, G., Bobrow, M., Bruce, M., Goedhert, M., McLean, A. and Webster, J. (2001). *Review of the Origin of BSE*. UK Department for Environment, Food, and Rural Affairs. Accessed: 2002. Available at: http://www.defra.gov.uk/animalh/bse/bseorigin.pdf.

Hourrigan, J., Klingsporn, A., Clark, W. W. and DeCamp, M. (1979). *Slow transmissible diseases of the central nervous system*, Academy Press, Nwe York.

Hsiao, K. and Prusiner, S. (1990). Inherited human prion diseases. *Neurology* **40**: 1820-1827.

Hsiao, K., Scott, M., Foster, D., DeArmond, S. J., Groth, D., Serban, H. and Prusiner, S. B. (1991). Spontaneous neurodegeneration in transgenic mice with prion protein codon 101 proline----leucine substitution. *Annals of the New York Academy of Sciences* **640**: 166-70.

Hsiao, K. K., Groth, D., Scott, M., Yang, S. L., Serban, H., Rapp, D., Foster, D., Torchia, M., Dearmond, S. J. and Prusiner, S. B. (1994). Serial transmission in rodents of neurodegeneration from transgenic mice expressing mutant prion protein. *Proceedings of the National Academy of Sciences of the United States of America* **91**(19): 9126-30.

Hueston, W. (1997). 62 FR 551-583: Substances Prohibited from Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed; Proposed Rule. 1997.

Hunter, N., Foster, J. D. and Hope, J. (1992). Natural scrapie in British sheep: breeds, ages and PrP gene polymorphisms. *Veterinary Record* **130**(18): 389-92.

Hunter, N., Goldmann, W., Benson, G., Foster, J. D. and Hope, J. (1993). Swaledale sheep affected by natural scrapie differ significantly in PrP genotype frequencies from healthy sheep and those selected for reduced incidence of scrapie. *Journal of General Virology* **74**(Pt 6): 1025-31.

Hunter, N., Goldmann, W., Smith, G. and Hope, J. (1994). Frequencies of PrP gene variants in healthy cattle and cattle with BSE in Scotland. *Veterinary Record* **135**(17): 400-3.

Hunter, N., Foster, J. D., Goldmann, W., Stear, M. J., Hope, J. and Bostock, C. (1996). Natural scrapie in a closed flock of Cheviot sheep occurs only in specific PrP genotypes. *Archives of Virology* **141**(5): 809-24.

Hunter, N. (1997a). PrP genetics in sheep and the applications for scrapie and BSE. *Trends in Microbiology* **5**(8): 331-4.

Hunter, N., Goldmann, W., Foster, J. D., Cairns, D. and Smith, G. (1997b). Natural scrapie and PrP genotype: case-control studies in British sheep. *Veterinary Record* **141**(6): 137-40.

Hunter, N., Moore, L., Hosie, B., Dingwall, W. and Greig, A. (1997c). Association between natural scrapie and PrP genotype in a flock of Suffolk sheep in Scotland. *Veterinary Record* **140**(3): 59-63.

Hunter, N. (1998a). Scrapie. *Molecular Biotechnology* **9**: 225-234.

Hunter, N. and Cairns, D. (1998b). Scrapie-free Merino and Poll Dorset sheep from Australia and New Zealand have normal frequencies of scrapie-susceptible PrP genotypes. *Journal of General Virology* **79**(Pt 8): 2079-82.

Ikeda, T., Horiuchi, M., Ishiguro, N., Muramatsu, Y., Kai-Uwe, G. and Shinagawa, M. (1995). Amino acid polymorphisms of PrP with reference to onset of scrapie in Suffolk and Corriedale sheep in Japan. *Journal of General Virology* **76**(10): 2577-81.

Ironside, J. W., Head, M. W., Bell, J. E., McCardle, L. and Will, R. G. (2000). Laboratory diagnosis of variant Creutzfeldt-Jakob disease. *Histopathology* **37**(1): 1-9.

Kelley, L. C., Hafner, S., McCaskey, P. C., Sutton, M. T. and Langheinrich, K. A. (2000). An evaluation of methods for the detection of spinal cord in product derived from advanced meat recovery systems. *Journal of Food Protection* **63**(8): 1107-12.

Kelly, D., Rearson, H., Wright, A. and Greenham, L. (1980). Morbidity in captive white tigers. *Comparative Pathology of Zoo animals*. R. Montali and G. Migaki. Washington DC, Institute Press: 183-188.

Kimberlin, R., Cole, S. and Walker, C. (1987). Temporary and permanent modifications to a single strain of mouse scrapie on transmission to rats and hamsters. *Journal of General Virology. 68 ( Pt 7):1875-81* **68**(7): 1875-81.

Kimberlin, R. H., Walker, C. A., Millson, G. C., Taylor, D. M., Robertson, P. A., Tomlinson, A. H. and Dickinson, A. G. (1983). Disinfection studies with two strains of mouse-passaged scrapie agent. Guidelines for Creutzfeldt-Jakob and related agents. *Journal of the Neurological Sciences* **59**(3): 355-69.

Kimberlin, R. H. and Walker, C. A. (1988). *Pathogenesis of experimental scrapie.* Novel infectious agents and the central nervous system-Ciba Foundation Symposium, Wiley, Chichester.

Kimberlin, R. H. and Walker, C. A. (1989). Pathogenesis of scrapie in mice after intragastric infection. *Virus Research* **12**(3): 213-20.

Kimberlin, R. H. (1990). Transmissible encephalopathies in animals. *Canadian Journal of Veterinary Research* **54**(1): 30-7.

Kimberlin, R. H. and Wilesmith, J. W. (1994). Bovine spongiform encephalopathy. Epidemiology, low dose exposure and risks. *Annals of the New York Academy of Sciences* **724**: 210-20.

Klatzo, I., Gajdusek, D. C. and Zigas, V. (1957). Pathology of kuru. *Laboratory Investigations* **8**: 799-847.

Laplanche, J., Chatelain, J., Westaway, D., Thomas, S., Dussaucy, M., Brugere-Picoux, J. and Launay, J. (1993). PrP polymorphisms associated with natural scrapie discovered by denaturing gradient gel electrophoresis. *Genomics* **15**(1): 30-7.

Lasmezas, C. I., Deslys, J. P., Robain, O., Jaegly, A., Beringue, V., Peyrin, J. M., Fournier, J. G., Hauw, J. J., Rossier, J. and Dormont, D. (1997). Transmission of the BSE agent to mice in the absence of detectable abnormal prion protein. *Science* **275**(5298): 402-5.

Lord Phillips, o. W. M., Bridgeman, J. C. and Ferguson-Smith, M. F. (2000). The BSE Inquiry.

Lucker, E., Eigenbrodt, E., Wenisch, S., Leiser, R. and Bulte, M. (2000). Identification of central nervous system tissue in retail meat products. *J Food Prot.* **63**(2): 258-63.

MAFF (Ministry of Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) (2000). *BSE: Measures Taken by the UK: Report for the Month to the End of August 2000.* Available at: http://www.defra.gov.uk/animalh/bse/bse-publications/monrep/monrep29.pdf.

MAFF (Ministry of Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) (2001a). *BSE information: Transmission of BSE (Infectivity in Tissues).* Accessed: 2003. Available at: http://www.defra.gov.uk/animalh/bse/bse-science/level-4-transmis.html#infect.

MAFF (Ministry of Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) (2001b). *BSE information: Transmission of BSE (Infectivity to Other Species).*

Available at: http://www.defra.gov.uk/animalh/bse/bse-science/level-4-transmis.html#species.

MAFF (Ministry of Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) (2001c). *BSE Information: Specified Risk Material*. Available at: http://www.defra.gov.uk/animalh/bse/public-health/level-3-srms.html.

Manson, J. C., Jamieson, E., Baybutt, H., Tuzi, N. L., Barron, R., McConnell, I., Somerville, R., Ironside, J., Will, R., Sy, M. S., Melton, D. W., Hope, J. and Bostock, C. (1999). A single amino acid alteration (101L) introduced into murine PrP dramatically alters incubation time of transmissible spongiform encephalopathy. *EMBO Journal* **18**(23): 6855-64.

Manuelidis, L., Sklaviadis, T., Akowitz, A. and Fritch, W. (1995). Viral particles are required for infection in neurodegenerative Creutzfeldt-Jakob disease. *Proceedings of the National Academy of Sciences of the United States of America* **92**(11): 5124-8.

Marsh, R. F., Burger, D., Eckroade, R., ZuRhein, G. M. and Hanson, R. P. (1969). A preliminary report on the experimental host range of transmissible mink encephalopathy agent. *J. Inf. Dis.* **120**: 713-719.

Marsh, R. F., Bessen, R. A., Lehmann, S. and Hartsough, G. R. (1991). Epidemiological and experimental studies on a new incident of transmissible mink encephalopathy. *Journal of General Virology* **72**(Pt 3): 589-94.

Masters, C. L., Harris, J., Gajdusek, C., Gibbs, C., Bernoulli, C. and Asher, D. M. (1978). Creutzfeldt-Jakob Disease: Patterns of Wordwide occurrence and the Significance of Familial and Sporadic Clustering. *Ann Neurol* **5**: 177-188.

McKenzie, D., Bartz, J., Mirwald, J., Olander, D., Marsh, R. and Aiken, J. (1998). Reversibility of scrapie inactivation is enhanced by copper. *Journal of Biological Chemistry* **273**(40): 25545-7.

McKinley, M. P., Bolton, D. C. and Prusiner, S. B. (1983). A protease-resistant protein is a structural component of the scrapie prion. *Cell* **35**(1): 57-62.

McLean, C. A., Ironside, J. W., Alpers, M. P., Brown, P. W., Cervenakova, L., Anderson, R. M. and Masters, C. (1998). Comparative Neuropathology of Kuru with New Variant Creutzfeldt Jakob Disease: Evidence of Strain of Agent Predominating over Genotype of host. *Brain Pathology* **8**: 429-437.

Miller, M., Williams, S., McCarty, C., Spraker, T., Kreeger, T., Larsen, T. and Thorne, E. (2000). Epizootiology of Chronic Wasting Disease in free-ranging cervids in Colorado and Wyaoming. *Jouranl of Wildlife Diseases* **36**(4): 676-690.

Miller, M. W., Wild, M. A. and Williams, E. S. (1998). Epidemiology of chronic wasting disease in captive Rocky Mountain elk. *Journal of Wildlife Diseases* **34**(3): 532-8.

Nathanson, N., Wilesmith, J. and Griot, C. (1997). Bovine spongiform encephalopathy (BSE): causes and consequences of a common source epidemic. *American Journal of Epidemiology* **145**(11): 959-69.

Nowak, R., Ronald and Paraiso, J. (1983). *Walker's Mammals of the World*, Johns Hopkins Univ. Press.

OIE (2000). Bovine spongiform encephalopathy. *http://www.oie.int/eng/info/en_esb.htm*.

OIE (2001). Surveillance and Monitoring of Bovine Spongiform Encephaolopathy. *http://www.oie.int/eng/normes/mcode/A_00154.htm*.

O'Rourke, K. I., Besser, T. E., Miller, M. W., Cline, T. F., Spraker, T. R., Jenny, A. L., Wild, M. A., Zebarth, G. L. and Williams, E. S. (1999). PrP genotypes of captive and free-ranging Rocky Mountain elk (Cervus elaphus nelsoni) with chronic wasting disease. *Journal of General Virology* **80**(Pt 10): 2765-9.

Palmer, M. S., Dryden, A. J., Hughes, J. T. and Collinge, J. (1991). Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease. [see comments]. [erratum appears in Nature 1991 Aug 8;352(6335):547]. *Nature* **352**(6333): 340-2.

Parchi, P., Giese, A., Capellari, S., Brown, P., Schulz-Schaeffer, W., Windl, O., Zerr, I., Budka, H., Kopp, N., Piccardo, P., Poser, S., Rojiani, A., Streichemberger, N., Julien, J., Vital, C., Ghetti, B., Gambetti, P. and Kretzschmar, H. (1999). Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Annals of Neurology* **46**(2): 224-33.

Pattison, I., Gordon, W. and Millson, G. (1959). The possible natural transmission of scrapie in goats. *Journal of Comparative Pathology* **71**: 101-108.

Platt, T. (2001). Executive Director, Fur Commission USA. Personal Communication.

Poulter, M., Baker, H. F., Frith, C. D., Leach, M., Lofthouse, R., Ridley, R. M., Shah, T., Owen, F., Collinge, J. and Brown, J. (1992). Inherited prion disease with 144 base pair gene insertion. 1. Genealogical and molecular studies. *Brain* **115**(Pt 3): 675-85.

Priola, S. A., Caughey, B., Race, R. E. and Chesebro, B. (1994). Heterologous PrP molecules interfere with accumulation of protease-resistant PrP in scrapie-infected murine neuroblastoma cells. *Journal of Virology* **68**(8): 4873-8.

ProMED-mail (2001, April 18). BSE trigger suspected to be African antelope.

Prusiner, S. (1989). Scrapie Prions. *Annu. Rev. Microbiol.* **43**: 345-74.

Prusiner, S. B. (1982). Novel proteinaceous infectious particles cause scrapie. *Science* **216**(4542): 136-44.

Prusiner, S. B. (1994). Biology and genetics of prion diseases. *Annual Review of Microbiology* **48**: 655-86.

Prusiner, S. B. (1998). Prions. *Proceedings of the National Academy of Sciences of the United States of America* **95**(23): 13363-83.

Public Citizen (2001). Letter to the USDA and FDA Re: BSE.

Purdey, M. (1996). The UK epidemic of BSE: slow virus or chronic pesticide-initiated modification of the prion protein? Part 2: An epidemiological perspective. *Medical Hypotheses* **46**(5): 445-54.

Race, R. and Chesebro, B. (1998a). Scrapie infectivity found in resistant species. *Nature* **392**(6678): 770.

Race, R., Jenny, A. and Sutton, D. (1998b). **Scrapie** infectivity and proteinase K-resistant prion protein in sheep placenta, brain, spleen, and lymph node: implications for transmission and antemortem diagnosis. *Journal of Infectious Diseases* **178**(4): 949-53.

Raymond, G., Hope, J., Kocisko, D., Priola, S., Raymond, L., Bossers, A., Ironside, J., Will, R., Chen, S., Petersen, R., Gambetti, P., Rubenstein, R., Smits, M., Lansbury, P. and Caughey, B. (1997). Molecular assessment of the potential transmissibilities of BSE and scrapie to humans. *Nature* **388**(6639): 285-8.

Raymond, G., Bossers, A., Raymond, L., O'Rourke, K., McHolland, L., Bryant, P., Miller, M., Williams, E., Smits, M. and Caughey, B. (2000). Evidence of a molecular barrier limiting susceptibility of humans, cattle and sheep to chronic wasting disease. *EMBO* **19**(17): 4425-30.

Rehbinder, C. and Petersson, L. (1994). Cerebellar abiotrophy in a moose (Alces alces L) related to copper deficiency. A case report. *Acta Veterinaria Scandinavica* **35**(1): 103-6.

Ridley, R. and Baker, H. (1996). The myth of maternal transmission of spongiform encephalopathy. *BMJ* **311**(7012): 1071-5.

Robinson, M. M., Hadlow, W. J., Knowles, D. P., Huff, T. P., Lacy, P. A., Marsh, R. F. and Gorham, J. R. (1995). Experimental infection of cattle with the agents of transmissible mink encephalopathy and scrapie. *Journal of Comparative Pathology* **113**(3): 241-51.

Rocky Mountain Elk Foundation (1997). Status of the Elk im North America 1975-1995.

Romans, J. and Ziegler, P. (1974). *The meat we eat.* Danville, Illinois, The Interestate Printers & Publishers Inc,.

Rudbeck, J. (1999). More Products Shipping Overseas but Cost Less. *Renderer, The National Magazine of the Rendererring*(October).

Ryder, S. J., Hawkins, S. A., Dawson, M. and Wells, G. A. (2000). The neuropathology of experimental bovine spongiform encephalopathy in the pig. *Journal of Comparative Pathology* **122**(2-3): 131-43.

Schaller, O., Fatzer, R., Stack, M., Clark, J., Cooley, W., Biffiger, K., Egli, S., Doherr, M., Vandevelde, M., Heim, D., Oesch, B. and Moser, M. (1999). Validation of a western immunoblotting procedure for bovine PrP(Sc) detection and its use as a rapid surveillance method for the diagnosis of bovine spongiform encephalopathy (BSE). *Acta Neuropathologica* **98**(5): 437-43.

Schmidt, G., Yemm, R. S., Childs, K. D., O"Callagham, J. P. and Hossner, K. L. (2001). Beta site analysis and verification of different glial fibrillary acidic protein (GFAP) analyses as accurate detectors of central nervous system tissue in advanced meat recovery (AMR) products. *In press.*

Schmidt, G. R., Hossner, K. L., Yemm, R. S., Gould, D. H. and O'Callaghan, J. P. (1999). An enzyme-linked immunosorbent assay for glial fibrillary acidic protein as an indicator of the presence of brain or spinal cord in meat. *Journal of Food Protection* **62**(4): 394-7.

Schreuder, B. C., Wilesmith, J., Ryan, J. B. M. and Straub, O. C. (1997). Risk of BSE from the import of cattle from UK into countries in the European Union. *Veterinary Record* **141**: 187-190.

Schreuder, B. E., Geertsma, R. E., van Keulen, L. J., van Asten, J. A., Enthoven, P., Oberthur, R. C., de Koeijer, A. A. and Osterhaus, A. D. (1998). Studies on the efficacy of hyperbaric rendering procedures in inactivating bovine spongiform encephalopathy (BSE) and scrapie agents. *Veterinary Record* **142**(18): 474-80.

Scott, M. R., Will, R., Ironside, J., Nguyen, H. O., Tremblay, P., DeArmond, S. J. and Prusiner, S. B. (1999). Compelling transgenetic evidence for transmission of bovine spongiform encephalopathy prions to humans. *Proceedings of the National Academy of Sciences of the United States of America* **96**(26): 15137-42.

Sigurdson, C. J., Williams, E. S., Miller, M. W., Spraker, T. R., O'Rourke, K. I. and Hoover, E. A. (1999). Oral transmission and early lymphoid tropism of chronic wasting disease PrPres in mule deer fawns (Odocoileus hemionus). *Journal of General Virology* **80**(Pt 10): 2757-64.

Sigurdson, S. (1991). Epidemiology of scrapie in Iceland with control measures. *Sub acute spongiform encephalopathies. Proceedings of an EC seminar, 12-14 November 1990*: 233-242.

Simmons, M. M., Ryder, S. J., Chaplin, M. C., Spencer, Y. I., Webb, C. R., Hoinville, L. J., Ryan, J., Stack, M. J., Wells, G. A. and Wilesmith, J. W. (2000). Scrapie surveillance in Great Britain: results of an abattoir survey, 1997/98. *Veterinary Record* **146**(14): 391-5.

Skarphedinsson, S., Johannsdottir, R., Gudmundsson, P., Sigurdarson, S. and Georgsson, G. (1994). PrPsc in Icelandic sheep naturally infected with scrapie. *Ann N Y Acad Sci* **724**: 304-9.

Southern States Cooperative (2001). Prices.

Sparks Companies, I. (1999). *Advanced Meat Recovery Systems - An Economic Analysis of the Proposed USDA Regulation*. McLean, VA Available at: http://www.fsis.usda.gov/OPPDE/rdad/FRPubs/98-027R/SparksCo_AMR_Economic_Analysis.pdf.

Spongiform Encephalopathy Advisory Committee (1997). Public summary of meeting on 24 October 1997.

Spongiform Encephalopathy Advisory Committee (1999a). *SEAC Annual Report 1997-1998* Available at: http://www.seac.gov.uk/seacrept.pdf.

Spongiform Encephalopathy Advisory Committee (1999b). *SEAC Annual Report 1998-1999* Available at: http://www.seac.gov.uk/98-9rep.pdf.

Spongiform Encephalopathy Advisory Committee (2000). *Risk Assessment for the disposal of treated rendering plant ruminant condensate to agricultural land.*

Stockman, S. (1913). Scrapie: An obscure disease of sheep. *Journal of Comparative Pathology.*

Stringer, S. M., Hunter, N. and Woolhouse, M. E. (1998). A mathematical model of the dynamics of scrapie in a sheep flock. *Mathematical Biosciences* **153**(2): 79-98.

Swiss Federal Veterinary Service (2002). Memo (March 18) to the Harvard Center for Risk Analysis: "Comments on the Harvard study: Evaluation of the potential for Bovine Spongiform Encephalopathy in the United States".

Taylor, D. M. (1989). Scrapie agent decontamination: implications for bovine spongiform encephalopathy. *Veterinary Record* **124**(12): 291-2.

Taylor, D. M. (1991a). Inactivation of the unconventional agents of scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. *Journal of Hospital Infection* **18 Suppl A**: 141-6.

Taylor, D. M. (1991b). Inactivation of BSE agent. *Developments in Biological Standardization* **75**: 97-102.

Taylor, D. M. (1993). Inactivation of SE agents. *British Medical Bulletin* **49**(4): 810-21.

Taylor, D. M., Woodgate, S. L. and Atkinson, M. J. (1995). Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. *Veterinary Record* **137**(24): 605-610.

Taylor, D. M. and Woodgate, S. L. (1997a). Bovine spongiform encephalopathy: the causal role of ruminant-derived protein in cattle diets. *Revue Scientifique et Technique* **16**(1): 187-98.

Taylor, D. M., Woodgate, S. L., Fleetwood, A. J. and Cawthorne, R. J. (1997b). Effect of rendering procedures on the scrapie agent. *Veterinary Record* **141**(25): 643-649.

Tegtmeier, C., Agerholm, J., Bille-Hansen, V., Schaap, P. and Ryder, S. (2001). Firs confirmed native case of bovine spongiform encephalopathy in Denmark. *Vet Rec* **148**: 51-52.

Telling, G. C., Scott, M., Mastrianni, J., Gabizon, R., Torchia, M., Cohen, F. E., DeArmond, S. J. and Prusiner, S. B. (1995). Prion propagation in mice expressing human and chimeric PrP transgenes implicates the interaction of cellular PrP with another protein. *Cell* **83**(1): 79-90.

Thornton, I. and Webb, J. S. (1979). Geochemistry and health in the United Kingdom. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **288**(1026): 151-68.

Tiwana, H., Wilson, C., Pirt, J., Cartmell, W. and Ebringer, A. (1999). Autoantibodies to brain components and antibodies to Acinetobacter calcoaceticus are present in bovine spongiform encephalopathy. *Infection & Immunity* **67**(12): 6591-5.

U.S. Department of Agriculture (1997). *Livestock and Carcass Disposition Review.* Food Safety Inspection Service.

U.S. Department of Agriculture (1998). *Animal Disposition Reporting System (ADRS) Livestock Slaughtered in USDA Establishments: Calendar Year 1998.* Food Safety Inspection Service. Accessed: 2001. Available at: http://www.fsis.usda.gov/OPHS/adrsdata/1998adrs/98crm1.htm.

U.S. Department of Agriculture (2000). *Scrapie Project Final Rule, 9 CFR Parts 54 and 79, Docket No. 99-067-2.* Animal Plant Health and Inspection Service. Accessed: 2000. Available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2000_register&docid=fr27jn00-3.

U.S. Department of Agriculture (2001a). *Factsheet: Chronic Wasting Disease Funding.* Animal and Plant Health Inspection Services. Available at: http://www.aphis.usda.gov/oa/pubs/cwdf.pdf.

U.S. Department of Agriculture (2001b). *Mink Annual Report.* NASS.

U.S. Department of Agriculture (2002). *Bovine Spongiform Encephalopathy: Surveillance.* Animal and Plant Health Inspection Services. Accessed: 2003. Available at: http://www.aphis.usda.gov/lpa/issues/bse/bse-surveillance.html.

U.S. Department of Agriculture (2003). *USDA Actions to Prevent Bovine Spongiform Encephelopathy.* Animal Plant Health Inspection Service. Accessed: 2003. Available at: http://www.aphis.usda.gov/lpa/issues/bse/bsechron.html.

U.S. Department of Agriculture (FSIS) (2002). *Revised Directive for Advanced Meat Recovery Systems.* Accessed: 2003. Available at: http://www.fsis.usda.gov/OA/background/amrdirec.htm.

U.S. Food and Drug Administration (1997). Substances prohibited from use in animal food or feed; Animal proteins prohibited in ruminant feed; Final Rule - 21 CFR Part 589. *Federal Register* **62**(108): 30935.

U.S. Food and Drug Administration (2001a). *Transmisible Spongiform Encephalopathy Advisory Meeting, March 19, 2001.* Available at: http://www.fda.gov/ohrms/dockets/ac/cber01.htm#Transmissible.

U.S. Food and Drug Administration (2001b). *January 10: Update on Ruminant Feed (BSE) Enforcement Activities.* Center for Veterinary Medicine. Accessed: 2001. Available at: http://www.fda.gov/cvm/index/updates/bseup.htm.

UK CJD Surveillance Unit (2003). *The UK Creutzfeldt-Jakob Disease Surveillance Unit.* Accessed: 2003. Available at: http://www.cjd.ed.ac.uk.

USDA-APHIS, V. S. (2000). Comments submitted by US on the "draft report on the assessment of the Geographical BSE-risk of the USA.

Venter, A. (2001). Mad deer in Canadian wild? *Trends in Microbiology* **9**(7): 312.

Vossen, P., Kreysa, J. and Goll, M. (2003). *Overview of the BSE Risk Assessments of the European Commission's Scientific Steering Committee (SSC) and its TSE/BSE ad hoc Group: Adopted Between September 1997 and April 2003*. Available at: http://europa.eu.int/comm/food/fs/sc/ssc/out364_en.pdf.

Walker, K. D., Hueston, W. D., Hurd, H. S. and Wilesmith, J. W. (1991). Comparison of bovine spongiform encephalopathy risk factors in the United States and Great Britain. *Journal of the American Veterinary Medical Association* **199**(11): 1554-61.

Warren, H. V. (1974). Proceedings: Environmental lead: a survey of its possible physiological significance. *Journal of Biosocial Science* **6**(2): 223-38.

Webb, C., Wilesmith, J., Simmons, M. and Hoinville, L. (2001). A stochastic model to estimate the prevalence of scrapie in Great Britain using the results of an abatoir based survey. *Preventive Veterinary Medicine* **51**: 269-287.

Weissmann, C. and Aguzzi, A. (1999). Perspectives: neurobiology. PrP's double causes trouble. *Science* **286**(5441): 914-5.

Wells, G. A., Wilesmith, J. W. and McGill, I. S. (1991). Bovine spongiform encephalopathy: a neuropathological perspective. *Brain Pathology* **1**(2): 69-78.

Wells, G. A., Hawkins, S. A., Green, R. B., Austin, A. R., Dexter, I., Spencer, Y. I., Chaplin, M. J., Stack, M. J. and Dawson, M. (1998). Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update. *Veterinary Record* **142**(5): 103-106.

Wells, G. A., Hawkins, S. A., Green, R. B., Spencer, Y. I., Dexter, I. and Dawson, M. (1999). Limited detection of sternal bone marrow infectivity in the clinical phase of experimental bovine spongiform encephalopathy (BSE). *Veterinary Record* **144**(11): 292-294.

Westaway, D., Zuliani, V., Cooper, C., DaCosta, M., Neuman, S., Jenny, A., Detwiler, L. and Prusiner, S. (1994). Homozigocity for prion protein alleles encoding glutamine-171 renders sheep susceptible to natural scrapie. *Genes and Development* **8**: 959-969.

WHO (2001). Fact Sheet: Bovine Spongiform Encephalopathy. *http://www.who.int/inf-fs/en/fact113.html*.

Wilesmith, J. and Ryan, J. B. M. (1992a). Bovine spongiform encephalopathy: Recent observations on the age-specific incidences. *Veterinary Record* **130**: 491-492.

Wilesmith, J. and Ryan, J. B. M. (1993). Bovine spongiform encephelopathy: Observations on the incidence during 1992. *Veterinary Record* **132**: 300-301.

Wilesmith, J. W., Wells, G., Cranwell, M. P. and Ryan, J. B. M. (1988). Bovine spongiform encephelopathy: Epidemiological studies. *Veterinary Record* **123**: 638-644.

Wilesmith, J. W., Ryan, J. B. and Atkinson, M. J. (1991). Bovine spongiform encephalopathy: Epidemiological studies on the origin. *Veterinary Record* **128**(9): 199-203.

Wilesmith, J. W., Ryan, J. B., Hueston, W. D. and Hoinville, L. J. (1992b). Bovine spongiform encephalopathy: epidemiological features 1985 to 1990. *Veterinary Record* **130**(5): 90-4.

Wilesmith, J. W. (1994). An epidemiologist's view of bovine spongiform encephalopathy. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences* **343**(1306): 357-61.

Wilesmith, J. W., Wells, G. A., Ryan, J. B., Gavier-Widen, D. and Simmons, M. M. (1997). A cohort study to examine maternally-associated risk factors for bovine spongiform encephalopathy. *Veterinary Record* **141**(10): 239-43.

Will, R., Matthews, W., Smith, P. and Hudson, C. (1986). A retrospective study of Creutzfeldt Jakob Disease in England and Wales 1970-1979. *Epidemilogy J. Neurol. Neurosurg. Psychiatry* **49**: 749-755.

Will, R. G., Ironside, J. W., Zeidler, M., Cousens, S. N., Estibeiro, K., Alperovitch, A., Poser, S., Pocchiari, M., Hofman, A. and Smith, P. G. (1996). A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* **347**(9006): 921-5.

Will, R. G., Zeidler, M., Stewart, G. E., Macleod, M. A., Ironside, J. W., Cousens, S. N., Mackenzie, J., Estibeiro, K., Green, A. J. and Knight, R. S. (2000). Diagnosis of new variant Creutzfeldt-Jakob disease. *Annals of Neurology* **47**(5): 575-82.

Williams, E. S. and Young, S. (1980). Chronic wasting disease of captive mule deer: a spongiform encephalopathy. *Journal of Wildlife Diseases* **16**(1): 89-98.

Williams, E. S. and Young, S. (1982). Spongiform encephalopathy of Rocky Mountain elk. *Journal of Wildlife Diseases* **18**(4): 465-71.

Williams, E. S. (2001). Department of Veterinary Sciences, University of Wyoming, Laramie. Personal Communication.

Wineland, N. E., Detwiler, L. A. and Salman, M. D. (1998). Epidemiologic analysis of reported scrapie in sheep in the United States: 1,117 cases (1947-1992). *Journal of the American Veterinary Medical Association* **212**(5): 713-8.

Woolhouse, M. E. and Anderson, R. M. (1997). Understanding the epidemiology of BSE. *Trends in Microbiology* **5**(11): 421-4.

Woolhouse, M. E., Stringer, S. M., Matthews, L., Hunter, N. and Anderson, R. M. (1998). Epidemiology and control of scrapie within a sheep flock. *Proceedings of the Royal Society of London - Series B: Biological Sciences* **265**(1402): 1205-10.

Zigas, V. and Gajdusek, D. C. (1957). Kuru: clinical study of a new syndrome resmbling paralysis agitans in native of the Eastern Higlands of Australian New Guinea. *Medical Journal of Australia* **2**: 745-754.