

**APHIS Response to Peer Review of the
Estimation of BSE Prevalence in the United States.**

July 20, 2006

Executive Summary

The document *An Estimate of the Prevalence of BSE in the United States*, prepared by the National Surveillance Unit of USDA:APHIS:VS, was completed April 27, 2006. The purpose of this document was to estimate the point prevalence of BSE in the U.S. as of March 17, 2006 based on surveillance data collected from 1999 to 2006. This document contained important scientific information and therefore it was subjected to a peer review in accordance with Office of Management and Budget (OMB) guidelines. This response to the peer review explains APHIS' agreement or disagreement with reviewer comments, the actions the agency will undertake, and the reasons the agency believes these actions satisfy any key concerns or recommendations in the report. At USDA request, RTI International (RTI) performed the peer review. RTI contracted with three independent reviewers, and RTI summarized the results in a report.

Reviewers were in agreement over the following issues:

- All reviewers agreed with the conclusion of the analysis that the estimated prevalence of BSE in the United States is less than 1 infected animal per million adult cattle.
- All reviewers found the BSurVE and Bayesian Birth Cohort (BBC) models statistically and epidemiologically sound.
- All reviewers agreed that APHIS appropriately considered key factors and that the models appear to be appropriately parameterized.
- Although each reviewer made suggestions to improve the model, all reviewers agreed that the prevalence estimate would likely be robust to the suggested changes.

The following reviewer requests for further analysis were identified by RTI:

1. Further consideration should be given to the representativeness of the sample set.
2. The effect of age distribution should be examined in the sensitivity analysis
3. Exit probabilities for infected cattle should be explored further in light of current European Union (E.U.) surveillance data.
4. Uncertainties with regard to the incubation period and age at infection should be given further consideration.

The four issues above were identified by RTI as warranting further consideration, so the response to the peer review focuses on these four issues. In addition, one reviewer emphasized suggestions regarding terminology used in the document. Because some of the suggested changes reflect jargon that differs between the reviewer's area of expertise (statistics) and jargon commonly used in the discipline of epidemiology, changes were made only where deemed appropriate to an epidemiological analysis. RTI reports that "a

couple of reviewers argued of the accuracy of using United Kingdom data to obtain the relative rate of decline in incidence in the United States in the BBC model, but they did not make a strong recommendation against using the current APHIS assumption.” Reviewer 1 says, *“At the same time, as previously noted, the results of the BBC model are not tremendously different than the baseline BSurvE results, suggesting that the USDA’s conclusion is robust relative to this assumption.”* Reviewer 2 states that, *“This is a reasonable assumption.”* APHIS acknowledges that this assumption may be worthy of future consideration but also agrees with the reviewers that the conclusion of the analysis is robust to this assumption. Therefore, no changes were made in the analysis.

Response to Specific Issues Identified by RTI

1. Representativeness.

Reviewer comments on the representativeness of the sample:

I believe the USDA needs to present a much more thorough consideration of how representative their sample set was, and whether this could have impacted the outcome or conclusions of the analyses. While the report states on page 11 that the BSurvE requires independence among samples but not that they are “randomly” selected, it is also emphasized that samples should be “representative” of the reference population.

He further clarifies the issue as follows:

What is the correct definition or interpretation of “representative” relative to this matter? I believe it implies that you would obtain approximately the same results if the sampling were conducted again. In this case because, there is an inherent assumption that the sampling was equally effective through all years of the surveillance program, it also implies that if the sampling were conducted again, moving sampling intensity from one part of the study to another, that you would also obtain essentially the same results.

APHIS response to reviewer considers temporal as well as geographic representation of the sample set.

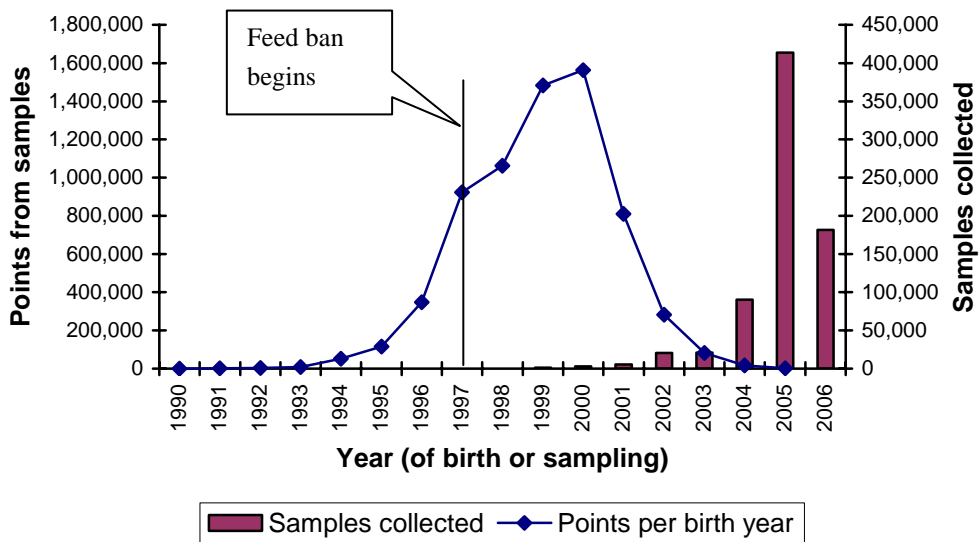
Temporal representativeness.

While speculation about the historic or future BSE prevalence in the United States is tempting, the goal of this analysis is to estimate the point prevalence of BSE as of March 17, 2006. Data collected over seven consecutive years were used for the estimation. These data represent animals born (exposed) over a longer period from the early 1990’s through 2005.

As shown in Figure 1, the largest number of samples were collected in 2004 to 2006 and the birth years of cattle sampled during this time were focused most intensively between 1994 and 2003 (i.e., animals 3 to 11 years of age). Since most BSE cases are infected in the same year they are born, these birth years represent the BSE exposure period for approximately 80% of the adult cattle population of the United States. If the enhanced surveillance had begun before 2004, the larger curve would undoubtedly have sampled

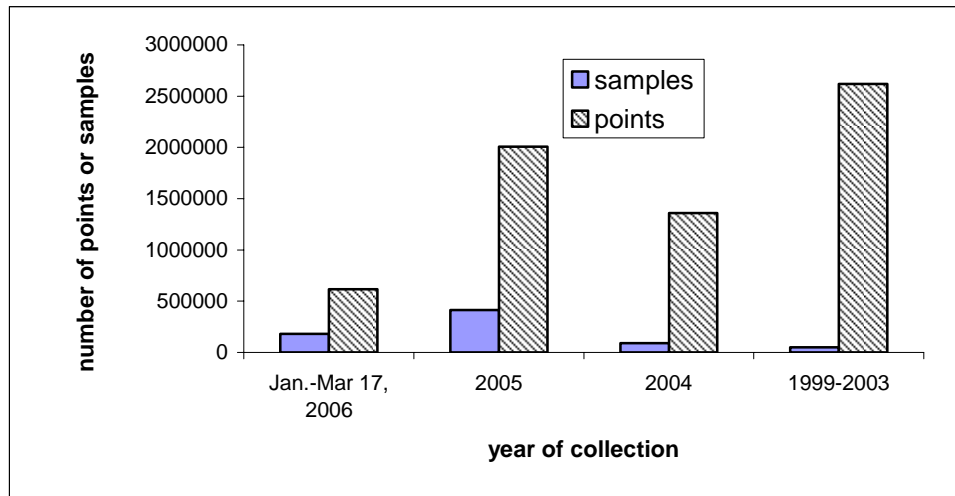
animals born in the late 1980's and early 1990's, with more intensity, however these samples would represent a very small portion of the U.S. standing population on March 17, 2006.

Figure 1. The bars on the right hand side of this figure represent the number of samples collected over a 7-year period. The curve (on the left hand side) demonstrates the number of analytic points (equivalent of random samples) (Wilesmith 2004) per birth year of animals in the sample (i.e., year of exposure). Note that the information gained from the samples collected is most representative of the time immediately before and after the feed ban. It is unlikely that prevalence would increase after this time (Cohen 2001, 2003)



Although sampling intensity was enhanced for the years 2004-2006, since 1993 the sampling strategy has been to test clinical suspects, which are the animals most likely to have BSE. These animals have been considered to be the preferable “target” for surveillance by OIE in the past and remain the preferred sample type in the current edition of the Code. Figure 2 below compares surveillance points from BSurVE with the number of samples collected. Although sampling intensity was greater during the enhanced surveillance, the number of points from the samples was substantial for the years before 2004 because of the high number of clinical suspect animals collected. This suggests that the surveillance sampling, if not equal in all years, was substantial and representative over the seven year period of data collection.

Figure 2. Although the number of BSE samples increased substantially in 2004, the information gained from them did not increase proportionately because U.S. surveillance has focused on the highest information value samples since 1992. Note that, although the majority of total samples and a large proportion of the points came from 2004-2006, the years between 1999 and 2003 are well represented.



Influence of geographic stratification in the analysis

Samples used in the prevalence analysis came from collection sites that comprise nationally representative avenues through which cattle may exit the adult cattle population and be available for sampling. While each type of collection site might draw greater numbers of samples from different parts of the national herd, every animal in the targeted population exiting the herd had an approximately equal opportunity of being selected by one or more of the collection site sources.

1. On-Farm

These samples were collected by accredited veterinarians, Federal or State employees (including animal health technicians), or VS-approved dead stock haulers. All animals meeting the definition of the targeted population in any location or production type were eligible for testing

2. Veterinary Diagnostic Laboratories

Cattle submitted for necropsy, or fresh whole brainstem submitted for ancillary diagnostics to veterinary diagnostic laboratories, including those not involved in BSE testing, were sampled by laboratory personnel. Because of the widespread availability of overnight mail and package delivery, diagnostic laboratories service nearly any location in the United States and all production types of animals.

3. Public Health Laboratories

Samples from cattle that were rabies suspects and test negative for rabies were submitted for BSE testing by laboratory personnel. All samples derived from this data source can be characterized as clinically suspicious for BSE, and thus are of high value to surveillance. Any animal demonstrating clinical signs compatible with rabies, regardless of location or production type, was eligible for submission for testing.

4. Slaughter (FSIS)

Cattle condemned at antemortem inspection were sampled by FSIS employees or designated off-site sample collection facilities. This sample source is not biased by location or production type because cull animals may be sourced from any state, including cull animals trucked to other locations.

5. Rendering or 3D/4D facilities

This sample source included animals that died and were not included in the cull slaughter category. Their representation is restricted to subpopulations that are within hauling distance of a rendering facility but were not otherwise biased by production type or national location. Areas without renderers would likely have samples collected through one of the other collections sites.

The BSE surveillance data represent a very large, targeted convenience sample covering all cattle producing regions in the country. The statistical limitations, however, do not necessarily indicate that the surveillance data are misallocated, either geographically or in some other manner. It only indicates that for operational reasons, the results lack some of the assurances typically built into statistical surveys to prevent potential biases.

However, the BSurvE model—upon which much of this analysis is based—requires only independence between observations, while its authors suggest a geographically balanced sampling (Wilesmith et. al., 2004). The follow excerpt from Wilesmith et. al. summarizes the BSurvE design to overcome these statistical limitations:

“Stock in each of the four surveillance streams is drawn from a sub-population of the standing population and represents a biased sample of the standing population with respect to age distribution, industry sector, BSE prevalence and ascertainment efficiency. The nature and extent of these biases vary both between the four surveillance streams and between countries. In other words, animals which die or are sent for slaughter cannot be considered as a random sample, representative of the animals which remain on farms, so it is not possible to use this data in a straightforward way to estimate BSE prevalence. The situation is further complicated by the long and variable incubation period of BSE, and the fact that current tests cannot detect the presence of disease until animals are late in the incubation period. ...

...Hence, in order to produce a useful estimate of the prevalence of BSE in the standing population of cattle, it is necessary to use an approach which takes account of all these complications, and works back from the surveillance data to

estimate BSE levels in animals which are still on farms, since it is these animals which will determine the future BSE trend in the country.”

Given apparent independence between observations and the intent to collect a geographically balanced sample, the U.S. surveillance effort meets the criteria for appropriate application of the BSurvE model.

The original sample size for each stratum was based on the assumption that the number of animals in the target population was a fixed proportion of the number of cows in the region. It further assumed proportionality between the percent of breeding cows within regions and the proportion of offspring born in the regions because the most relevant place to consider an animal to have originated from is the region where the cattle were likely infected; i.e., where they were born and/or spent their first year of life.

Although the results suggest differences between the planned and realized number of samples for each region, such a result is misleading. One factor that is often not fully appreciated is the degree to which animals move between States during their lifespan. In two States where back-tag information from slaughtered cattle was available (Georgia and Idaho), the number of adult cattle slaughtered was compared to the state of origin (i.e., state where back-tag was applied). Between 25 percent and 33 percent of these cattle were slaughtered in their state of origin. The remaining animals represented nearly all 50 States (personal communication APHIS/VS/CEAH). Thus, while it would be possible to treat the data as if they were a geographically stratified sample, the assumption of independence between strata would be difficult to justify.

The common movement of cattle between states and regions at different stages of production, and the frequent practices of purchasing, retagging, and dry lot feeding or re-shipping to cull slaughter plants in different states may preclude ready identification of the birth location of cattle. Thus, it is difficult to demonstrate the proportionality of estimated regional versus collected samples for all animals tested. Nonetheless, a qualitative understanding of the epidemiology of cattle management and movement suggest that the samples were not geographically biased because the sources of samples were designed to capture information from all sectors of cattle in the high risk population.

If we accept that sampling was proportional to birth region, then the question arises: how is variance estimation affected by ignoring the stratification of the sampling effort? The following derivation is given to show that ignoring the original stratification will have little effect on the variance of the estimator. Assume that the original sample of n animals was stratified into six subpopulations based on the density of breeding cows in each region of the country. In this situation the sample size in each stratum was determined by proportional allocation, so that $\frac{n_h}{n} = \frac{N_h}{N}$, where N_h and N are the number of animals in each region and the total number of animals, respectively. When estimating a proportion, the population variance in each stratum is $S_h^2 = P_h(1 - P_h)$, so the sample variance in

each stratum is $V(\hat{P}_h) = \frac{S_h^2}{n_n}$. A key assumption is that the prevalence in each region is the same. Based on the available data, there is no reason to believe that prevalence is significantly different between geographic regions. Comparing the point values of data collected from the six regions (by region of last residence) involves 15 pair-wise comparisons ($c = \frac{6 \times (5)}{2} = 15$). To maintain an overall type I error (false positive) rate of 0.05, the comparison-wise type I error rate (CER) is set to CER = 0.0034 (Sidak 1967):

$$\text{CER} = 1 - (1 - 0.05)^{1/c}$$

Because the confidence intervals for the associated Beta distributions overlap (Figure 3), a multiple comparisons test provides no empirical basis for concluding that prevalence is statistically different between regions.

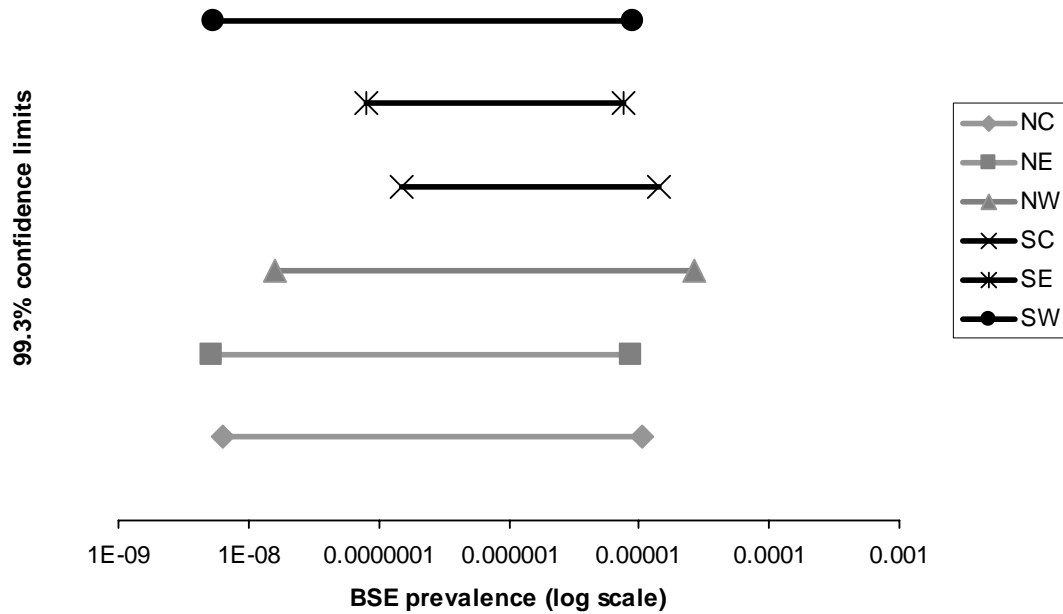


Figure 3. Multiple comparisons of BSE prevalence uncertainty for surveillance completed in six U.S. regions. This graphic demonstrates that the 99.3% confidence levels for prevalence overlap for all six regions, thereby supporting a conclusion that there is no statistical evidence of differences in prevalence between regions. NC=North Central, NE=Northeast, NW=Northwest, SC=South Central, SE=Southeast, SW=Southwest

Assuming that the prevalence is equal in each region, then $P_h = P$ and $S_h^2 = S_w^2$ for all six strata. Under these assumptions, the variance for a stratified sampling estimator under proportional allocation is

$$\begin{aligned}
 V(\hat{P}) &= \sum_{h=1}^6 \frac{W_h^2}{n_h} S_h^2 = S_w^2 \sum_{h=1}^6 \frac{W_h^2}{n_h} \\
 &= S_w^2 \sum_{h=1}^6 \frac{N_h^2}{N^2} \frac{1}{n_h} \\
 &= S_w^2 \sum_{h=1}^6 \frac{n_h^2}{n^2} \frac{1}{n_h} \\
 &= \frac{S_w^2}{n} \sum_{h=1}^6 \frac{n_h}{n} \\
 &= \frac{S_w^2}{n}
 \end{aligned}$$

To complete the argument, all that remains is to show that $S_h^2 \cong S_w^2$ in all cases. This is rather obvious because variance is the average squared distance between the observations and the population mean. If the mean is the same in each stratum and the responses are binary, there cannot be any difference. To show this, consider decomposing the variance using the usual between-and within-stratum sum of squares formula. This gives

$$\begin{aligned}
 (N-1)S^2 &= \sum_{h=1}^H \sum_{i=1}^{N_h} (y_{hi} - \bar{Y})^2 \\
 &= \sum_{h=1}^H \sum_{i=1}^{N_h} (y_{hi} - \bar{Y}_h)^2 + \sum_{h=1}^H N_h (\bar{Y}_h - \bar{Y})^2 \\
 &= \sum_{h=1}^H \sum_{i=1}^{N_h} (N_h - 1) S_h^2 + \sum_{h=1}^H N_h (\bar{Y}_h - \bar{Y})^2 \\
 &\cong S_h^2 \sum (N_h - 1) \text{ because } \bar{Y}_h = \bar{Y} \\
 &= (N - H) S_h^2, \text{ which implies} \\
 (N - 1) S^2 &\cong (N - H) S_h^2
 \end{aligned}$$

For this application, $(N - 1) \cong (N - H)$, so $S^2 \cong S_h^2 = S_w^2$ under the assumption used above. Thus, the variance of the stratified sampling estimator should be nearly identical to the variance of a simple random sample for this application.

The OIE terrestrial Animal Code, BSE Surveillance appendix (3.8.4.2), indicates that a country should “... ensure that samples are representative of the herd of the country, zone or compartment, and include consideration of demographic factors such as production type and geographic location, and the potential influence of culturally unique husbandry practices.” The APHIS prevalence analysis and the Summary Analysis document that is cited in the prevalence analysis considers geographic and production

type representativeness and found no evidence of unique cultural factors that would influence prevalence. The OIE Code also indicates that: “*The total points for samples collected may be accumulated over a period of a maximum of 7 consecutive years to achieve the target number of points determined in Table 1.*” It does not in any way suggest that temporal representativeness is a feature of the surveillance other than the requirement for a maximum period of collection over 7 years.

Since the reviewer indicates that he is unsure of the meaning of “representativeness” and provides his temporal interpretation, APHIS chooses to respond to his comment in the above text, but does not believe that temporal representativeness is required or suggested by international surveillance guidelines. Therefore no changes were made to the text of the analysis document.

2. Age Distribution

Reviewer comments on cattle ages:

I was concerned about several issues relative to the age used for the surveillance population. First, as noted in the “Enhanced Surveillance Report”, age data were collected categorically for animals sampled early in 1999-2003, and the USDA assumed that the true age distribution was represented by the age distribution for samples collected through the Enhanced Surveillance period. I believe further justification is warranted given that the sampling strategies were very different between early and later parts of the surveillance period.

Second, I believe that it may be invalid to assume that ages of cattle in the surveillance population can be estimated or approximated with precision using 1-year age increments up to the age of 17. Table 1 from the “Enhanced Surveillance Report” shows that nearly half of the samples collected for this period were obtained from renderers, which most likely would be collecting cattle that would be recorded as being dead with no other signs, and therefore would be allocated to the fallen stock surveillance stream. Examining the age-specific scheme for point allocation, it can be seen that 5 year old cattle receive the most points for all surveillance streams. While the exact age for cattle may have been requested during the Enhanced Surveillance period, I believe these data were biased as it is essentially impossible to accurately age cattle after they reach approximately 5 years of age using only externally visible physical parameters. The most common method used to estimate the age of cattle is by examining the dentition. Once all 8 permanent incisors have erupted and are in wear (usually assumed to occur at approximately 5 years of age), it becomes very difficult to accurately age cattle until they have begun to lose or wear out these teeth when it might be reasonably assumed that they have reached some advanced age. As such, I believe it may have been more reasonable to group surveillance data into age categories rather than to assume it was valid to report age in 1 year increments. I recommend that the USDA reconsider what the impact might have been regarding this potential misclassification.

APHIS response to reviewer comments on cattle ages:

With regard to categorical recording of ages, the reviewer seems to have misinterpreted our description of age determination in the document titled *Summary of Enhanced BSE Surveillance in the United States* (APHIS 2006). Ages were recorded categorically only for a brief period from June 1, 2004 through Oct. 24, 2004. Prior to June 1, 2004, and after Oct. 24, 2004, ages were recorded in a continuous fashion in years or months.

Ages were imputed in circumstances in which age was unknown or for those ages recorded categorically as “5 years or older” or “adult-could not determine age.” For samples collected during the years 1999-2003, ages were imputed based solely on the distribution of recorded ages for samples collected during that specific fiscal year. For example, unknown ages from samples collected during 2001 were imputed based on the age distribution for samples collected during fiscal year 2001. For samples collected during the Enhanced Surveillance period, unknown ages were imputed based on the age distribution of samples collected during the entire Enhanced Surveillance Period. For samples collected during fiscal year 2004, which encompassed both the pre-Enhanced and Enhanced Surveillance periods, imputations for samples collected through May 31, 2004 were based on samples collected through May 31, 2004, and imputations for samples collected on or after June 1, 2004 were based on the entire Enhanced Surveillance period.

The reviewer’s second concern with respect to cattle ages relates to the inability to accurately age cattle 5 years old and above based on dentition, which could lead to misclassification of ages for cattle 5 and above. We agree with the reviewer that this could influence the outcome of the analysis, and have added a section addressing the issue to the Sensitivity Analysis in the final document. Because age determination of cattle by changes in dentition becomes increasingly less precise after age 5 years, the possibility exists that the reported ages of cattle in the surveillance data were incorrectly recorded. Redistributing the reported ages for cattle 5 years and above to parallel the distribution of cattle aged 5 and above in the standing population resulted in a more even distribution of samples across the ages 5-17. However, this had little effect on prevalence estimates (Table 1).

Table 1. Results from the BSurvE Prevalence B model and BBC model after redistributing the reported ages of animals of cattle 5 years and older to parallel the age distribution of the standing adult cattle population. The results are shown as the mean and 90% confidence interval.

	<i>BSurvE Prevalence B model</i>	<i>BBC model</i>
BSE Prevalence estimate results in the U.S.	7 (3 , 24)	4 (1 , 8)
Redistributing age of cattle 5 years and older to parallel standing adult population	10 (4 , 32)	6 (2, 11)

3. Exit Probabilities for Infected Cattle

Reviewer comments on exit probabilities for infected cattle:

Because of lack of data specific for the US (with regard to exit constants for uninfected and infected cattle $d_{j,i}$ and $c_{j,i}$) the default values in the BSurvE model were used. The default estimates of the exit probabilities as done in the BSurvE model are somewhat problematic. First, there is no clear explanation or justification for the estimates in the documentation or instructions for the BSurvE Model (Wilesmith et al., 2005; Wilesmith et al., 2004) only that they were derived from UK or EU data. Theoretically, the vast majority of cattle over 24-30 months of age are tested in the EU countries. In 2004, the percentage of BSE tests done in the surveillance streams healthy slaughter, fallen stock, emergency slaughter and clinical suspects were about 88%, 10%, 0.7% and 0.03%, respectively (EC, 2005). The BSurvE suggests that 89%, 7%, 4% and 0.09% would enter the respective surveillance streams. The BSurvE estimates seem reasonable in this case.

The percentage of BSE cases in the EU in 2004 found in the surveillance streams healthy slaughter, fallen stock, emergency slaughter and clinical suspects were about 29%, 49%, 23% and 18%, respectively [in a request for clarification, the reviewer corrected these numbers to approximately 29%, 49%, 2%, and 20%]. However, the default values in the BSurvE model suggest that about 17%, 10%, 10% and 64% of the BSE cases would be found in the respective surveillance streams (see table 9 in the Parameters worksheet). It appears to me that something is wrong here. It seems to me that the surveillance stream where the BSE cases are actually found in a near total surveillance system should be a better estimator of the exit probabilities than those provided in the BSurvE model. It is somewhat surprising that differences of this magnitude would not have a significant effect on the prevalence estimates. Lack of time prevents me from determining what effect changes in the exit constants would have on the US prevalence estimate. I encourage the authors to explore this further. Thorough analysis of the EU BSE testing data may be useful.

APHIS response to reviewer comments on exit probabilities:

The E.U. values cited by the reviewer represent all infected animals exiting the population while the BSurvE values represent only those infected cattle showing clinical signs. This distinction, coupled with the E.U.'s fairly restrictive definition of clinical suspects, precludes direct use of the E.U. data as BSurvE inputs. It is arguable whether

the 2004 E.U. data is more or less appropriate than the BSurvE authors' estimates for the surveillance stream exit constants that were based on expert opinion and available U.K. and E.U. data. However, we concur with the reviewer that basing the exit constants for infected cattle on current E.U. data is one valid alternative to using the values estimated by the BSurvE authors. Because the reviewer's point was deemed worthy of further consideration, it is considered in the sensitivity analysis of the final document.

The BSurvE values for $c_{j,t}$ (5 percent, 10 percent, 10 percent, and 75 percent for healthy, fallen stock, casualty slaughter and clinical suspect surveillance streams, respectively), were derived from a combination of U.K. and E.U. data, as well as expert opinion (D. Prattley, personal communication, 2006). Based on 2004 E.U. data (after subtraction of U.K. results) exit fractions for the healthy slaughter, fallen stock, casualty slaughter and clinical suspect streams were 29 percent, 49 percent, 2 percent, and 20 percent, respectively, and these values were used for $c_{j,t}$ in place of the aforementioned 5 percent, 10 percent, 10 percent, and 75 percent for healthy, fallen stock, casualty slaughter and clinical suspect surveillance streams, respectively. Despite the substantial reduction in fraction of infected cattle exiting via the clinical suspect stream in this alternative scenario, the resulting estimated prevalence is only slightly increased (Table 2).

Table 2. Results from BSurvE Prevalence B and BBC models using 2004 E.U. data suggested by reviewer 2. Results are presented as mean values with 90% confidence interval.

	<i>BSurvE prevalence B model</i>	<i>BBC model</i>
BSE Prevalence estimate results in the U.S.	7 (3, 24)	4 (1, 8)
Results using 2004 E.U. data for $c_{j,t}$ suggested by reviewer 2	9 (4, 28)	7 (2, 15)

4. Uncertainties with regard to the incubation period

Reviewer comments on uncertainties with regard to the incubation period:

There are some uncertainties that have not been identified and analyzed including the age at infection distribution and the incubation period distribution. The use of a different age at infection assumption or a different incubation period distribution would have an effect on the prevalence estimates.

APHIS response to reviewer comments on incubation period uncertainties:

We agree that the use of a different age at infection assumption or a different incubation period distribution may result in changes in the prevalence estimates. However, we disagree with the suggestion that age at infection be given further consideration in the sensitivity analysis. There is strong support in the scientific literature for the BSurvE

assumption that susceptibility to BSE peaks in cattle less than one year old and then decreases exponentially (Cohen et al., 2001, 2003; de Koeijer, 1999; Woolhouse, 1997). Additionally, the Harvard-Tuskegee study indicates that the dose required for an older animal to become infected is much higher than for cattle less than one year old, making infection in older cattle far less probable, particularly in a country with a low prevalence.

The effect of incubation period distribution has already been addressed in the sensitivity analysis under the description of the C_t parameter. C_t refers to the age at which infected cattle will exit the population. Since cattle are assumed to be infected during their first year of life, increases in C_t are equivalent to increasing the incubation period. The following text, which is quoted from the peer-reviewed document, addresses the issue of incubation period:

The sensitivity coefficient for C_t suggests that BSE prevalence estimated by BSurvE will increase by approximately 3.3 percent for a 1 percent increase in the mean of the latency period. Increasing the average age that infected cattle exit the population (latency period) will generally reduce the point values of samples and, correspondingly, cause the surveillance information to support a somewhat larger prevalence. On the other hand, increasing the standard deviation by 1 percent increases the spread of the distribution and results in almost a 1 percent decrease in prevalence. The sensitivity coefficients for these inputs were low, so changing these inputs would not result in disproportionately large changes in prevalence.

Because this parameter is strongly supported in scientific literature and is already examined in the sensitivity analysis, APHIS did not take further action on this comment.

References

APHIS (2006). USDA:APHIS: VS, CEAH. Summary of Enhanced BSE Surveillance in the United States, April 28, 2006.

Cohen JT, Duggar K, Gray G, Kreindel S, Abdelrahman H, HabteMariam T, Oryang D, Tameru B. (2001) Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States. Harvard Center for Risk Analysis/Harvard School of Public Health and Center for Computational Epidemiology, College of Veterinary Medicine, Tuskegee University. November 2001, (revised October 2003). Available at <http://www.aphis.usda.gov/lpa/issues/bse/madcow.pdf>

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

EC (European Commission). (2005) Report on the Monitoring and Testing of Ruminants for the Presence of Transmissible Spongiform Encephalopathy (TSE) in the EU in 2004. http://europa.eu.int/comm/food/food/biosafety/bse/annual_report_tse2004_en.pdf

Sidak Z (1967) Rectangular Confidence Regions for the Means of Multivariate Normal Distributions. *Journal of the American Statistical Association* 62:626-633.

Wilesmith J, Morris R, Stevenson M, Prattley D, Cannon R, Benard H (2005). BSurVE: A Model for Evaluation of National BSE Prevalence and Surveillance. User instructions for the BSurVE model, Version 05.04b, April 2005. Weybridge, England. Veterinary Laboratories Agency.

Wilesmith J, Morris R, Stevenson M, Cannon R, Prattley D, and Benard H (2004) Development of a Method for the Evaluation of National Surveillance Data and Optimization of National Surveillance Strategies for Bovine Spongiform Encephalopathy. Weybridge, England, European Union TSE Community Reference Laboratory, Veterinary Laboratories Agency.

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