

Testimony of George M. Gray
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Committee on Government Reform
Committee on Agriculture
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Chairman Davis, Chairman Goodlatte, members of the Committee, thank you for the opportunity to appear before you today. I am George M. Gray, Ph.D., Executive Director of the Harvard Center for Risk Analysis. You can learn more about our Center, its mission, research, and funding at our website (<http://www.hcra.harvard.edu/>). My comments today are based on my research and experience as a scientist, risk analyst, and public health professional. These comments are my own and should not be attributed to the Harvard Center for Risk Analysis or to the Harvard School of Public Health. I do want to recognize the contribution of my colleague, Dr. Joshua T. Cohen, to the work on which this testimony is based. Part of this testimony is based on our March, 2004 review of the USDA Enhanced BSE Surveillance Plan, a copy of which is attached to my testimony.

I want to make 3 main points today:

- First, surveillance provides useful information for deciding the appropriateness and extent of risk management efforts, but it is not a public health or animals protection measure;
- Second, USDA's plan to focus on high risk animals is the most efficient and effective way to conduct surveillance; and
- Finally, there will be challenges to using the information generated by the surveillance program to estimate the possible extent of BSE in the United States, but these issues can be addressed.

I turn now to my first point – that the surveillance information helps us to manage risk. Surveillance does so by helping us to understand whether BSE is present in the U.S. cattle herd and how extensively it may have spread. The U.S. government has already taken many steps to reduce the risk of BSE to animals and humans. Surveillance helps us to determine if those measures have been successful, and whether additional – or fewer – measures are needed going forward.

It must be recognized that surveillance itself does not protect animal health or human health. Bovine Spongiform Encephalopathy (BSE) has a long incubation period, meaning that there can be a long period of time between the point when an animal becomes infected and the point when it exhibits clinical signs of disease. Because there are no known tests that can detect disease until just before the appearance of clinical signs, tests can miss animals that have BSE. Tests therefore offer limited protection against contamination of human food and animal feed. Instead, these risks have been addressed by USDA to remove high risk animals and tissues from human food and by FDA acting to reduce the risk of BSE spread among cattle. Surveillance only helps us to identify and quantify the problem.

My second point is that USDA's focus on testing high risk animals is the best way to monitor the population. Of course, the most accurate estimate of the number of animals with BSE could be developed if we tested every animal in the U.S. But much of the energy that would go into testing apparently healthy animals would not be productively spent.

For example, data from Europe¹ tell us that over the last two years the prevalence of BSE in high-risk animals has been about 25 times higher than the prevalence in apparently healthy animals over 30 months of age. That means that in Europe, where almost all experts agree BSE is a much more serious problem than it is in the U.S., testing 1,300 high risk animals is sufficient to find a single case of BSE with high probability. To find a single case of BSE among apparently healthy animals over 30 months of age with the same probability, more than 33,000 animals must be tested. Clearly, with limited resources, including testing facilities, USDA's focus on high-risk animals is the most effective and efficient way to test for the presence of BSE in the United States.

My final point has to do with the challenges involved in interpreting the results of a surveillance program that focuses on high risk animals. In particular, how do we extrapolate the findings from the high risk population, which USDA's Expanded Surveillance Plan appropriately focuses on, to apparently healthy animals? In the February, 2004 version of that plan, USDA estimated that if no additional animals with BSE were discovered after testing some 268,000 high risk animals and 20,000 apparently healthy animals, we could be 99% sure that the prevalence of BSE among slaughtered animals and animals that die would be no more than one in 10 million.

Dr. Cohen and I expressed some concerns about the assumptions underlying this estimate and offered a strategy for modifying the calculations to address these concerns. In particular, we explained that the prevalence rate in the apparently healthy population can be estimated by scaling down the measured prevalence in the high risk population. Weighting the two prevalence rates to reflect the sizes of these two populations yields a prevalence for the entire U.S. cattle herd. While the revised calculations will yield somewhat higher estimates for the total number of BSE cases in the U.S., we believe they will continue to show that the Expanded Surveillance Plan can detect BSE even if the prevalence is very low.

Our memo also points out that there are two ways to define the prevalence of BSE. One way would be to include only animals that have had BSE for a long enough period of time so that it can be detected by testing. Using that definition would have the advantage of making our prevalence estimates comparable to those reported by other countries, which also effectively exclude animals that have had BSE for too short a period of time for it to be detectable. Focusing on the detectable animals also makes sense because they have a much greater amount of infectivity than non-detectable animals and therefore pose a much greater risk to animals and humans. Alternatively, we could include in our estimate of prevalence all animals with BSE, including those that have not had the disease long enough for it to be detectable by testing. We described in our memo how the number of such animals could be estimated mathematically. The number of animals with undetectable BSE can be important because the incubation period for BSE can last many years and the disease is detectable by testing only near the end of this period.

I close with two concerns about our testing program. The first is the difficulty that the U.S. and the rest of the world have in dealing with countries when BSE is detected. The draconian act of completely shutting down trade makes the discovery of a BSE case such a major event that it creates possible disincentives to test thoroughly. The international community must come to agreement about ways to distinguish in trading decisions between countries with 10, 100, 1000, or 100,000 BSE cases. With appropriate risk management measures we should still be able to trade while protecting

¹ The following discussion is based on EUROPEAN COMMISSION - HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL (2004) REPORT ON THE MONITORING AND TESTING OF RUMINANTS FOR THE PRESENCE OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY (TSE) IN THE EU IN 2003, INCLUDING THE RESULTS OF THE SURVEY OF PRION PROTEIN GENOTYPES IN SHEEP BREEDS. 04-D-420525

human and animal health. This approach will also reduce incentives to hide possible cases and increase our ability to characterize BSE levels around the world.

My second concern is the way in which the results of the Expanded Surveillance Plan and the risks of BSE are communicated to the public, especially if another case is detected. A very important result from the analysis that we conducted² is that measures taken by the government, primarily the feed controls enacted by FDA in 1997, would reduce the prevalence of BSE in this country if it were introduced. However, we would need ongoing surveillance to demonstrate a decreasing prevalence over time. At this time no follow-up surveillance is planned. In addition, this follow-up would be very difficult and expensive and plagued by uncertainty given the low level of BSE likely to be found in the U.S. These factors will complicate the risk communication that must accompany discussions of the surveillance effort.

In summary, the USDA Expanded Surveillance Plan will provide useful knowledge for BSE risk management. However, it is important to remember that protecting human and animal health depends on other measures, many of which have been adopted or proposed by the relevant government agencies. These steps by USDA and FDA have already reduced BSE risks to humans and cattle. The Expanded Surveillance Plan as designed is targeted, efficient and will provide useful information. There will be challenges in interpreting and communicating the results, but I am confident that these challenges can be met.

Thank you for the opportunity to address you today. I will be happy to answer any questions.

² Cohen, J. T., Duggar, K., Gray, G. M. and Kreindel, S. (2003). *Evaluation of the Potential for Bovine Spongiform Encephalopathy in the United States: Report to the U.S. Department of Agriculture (revised October, 2003)*. Boston, MA, Harvard Center for Risk Analysis. Available at: <http://www.hcra.harvard.edu/pdf/madcow.pdf>.

Harvard Center for Risk Analysis

To: Ron DeHaven, Deputy Administrator, Veterinary Services, APHIS
From: Joshua Cohen and George Gray, Harvard Center for Risk Analysis
Date: March 12, 2004
Re: Comments on USDA bovine spongiform encephalopathy (BSE) surveillance plan

At the request of USDA, the Harvard Center for Risk Analysis has reviewed the Department's draft surveillance plan (USDA, 2004) designed to better estimate the prevalence of BSE in the U.S. cattle population. The draft plan addresses a number of issues, including the number of animals to test for BSE, which types of animals to test, sample collection logistics, costs, and communications. Our comments provide advice on how to best use the information gathered by surveillance for the purpose of estimating the overall prevalence of BSE in the U.S. cattle population. While we do not have the technical expertise to address other issues relevant to the plan, USDA's treatment of these issues seems appropriate to us.

In summary, we agree with USDA's focus on testing high risk cattle. If there are additional BSE-infected animals in the U.S., the likely high false negative rate for laboratory detection of BSE in normal adults and juveniles (animals that do not yet show signs of disease) would make a focus on these populations inefficient. The main interpretation challenge for USDA is the extrapolation of test results from the high risk cattle population to normal adult and juvenile cattle. Doing so requires the development of explicit assumptions about how the BSE prevalence rates in these sub-populations are related. We propose an approach and develop some initial estimates for these assumptions.

Before proceeding, we note that estimating the prevalence of BSE requires further consideration of USDA's goals. On the one hand, USDA could choose to estimate the prevalence detectable BSE in the U.S. cattle population. Here, we refer to the fact that current tests can only detect BSE near the end of the disease incubation period. Such an approach would not account for animals that are infected but have disease that is not detectable. These estimates have the advantage of being comparable to estimates reported by other countries, which also report the prevalence of detectable BSE. The detectable animals also pose a much greater risk than non-detectable animals because they have a much greater amount of infectivity. We describe how both prevalence rates can be estimated.

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As we understand it, USDA's plan proposes the laboratory testing of as many high risk cattle as is practical (amounting to 268,444, based on statistical and other considerations), and 10,000 adult cattle that are clinically normal. The high risk population represents 445,886 cattle, including 251,532 adult cattle that die on the farm, 194,225 satisfying FSIS condemnation criteria (non-ambulatory cattle, cattle with CNS signs and/or rabies negative, cattle with other signs potentially associated with BSE, and dead cattle), and 129 foreign disease investigation animals.

USDA explains that its sampling of the high risk population is sufficient to detect a prevalence rate of one case in 10 million, which when applied to the entire population of adult cattle (45 million), corresponds to a total prevalence of approximately five animals. USDA does not explicitly quantify the prevalence rate that could be detected by its sampling of 10,000 normal adult cattle, but using their calculations (which are based on formulas described by Cannon and Roe (1982)), we calculate that they can detect a prevalence rate of 3×10^{-4} with 95% certainty.

We note that USDA's derivation of a sensitivity level for their surveillance plan (one in 10 million animals with 99% certainty) assumes that all the infected animals in the U.S. belong to the high risk population group. In particular, USDA correctly calculated that the proposed plan would detect the presence of BSE with 99% certainty if as many as five high risk cattle had BSE. Dividing five into the adult cattle population size of 45 million yields approximately one in 10 million. However, because there may be BSE-infected animals in the normal adult and normal juvenile populations, a more rigorous set of assumptions must be developed to estimate a prevalence for the entire population.

For the purpose of quantifying the relationship between prevalence among high risk cattle and prevalence in the normal adult and normal juvenile sub-populations, we first define the population of interest to be those cattle that die or are slaughtered each year. For the purpose of quantifying the prevalence rate for the entire cattle population (including those that are alive), this definition leads to an upper bound because cattle that are slaughtered or that die are at higher risk for BSE than cattle that continue to live because the former have lived longer and have had more opportunities to be exposed to the BSE agent. On the other hand, for the purpose of quantifying the total prevalence (number of BSE positive cattle) for the entire cattle population, our definition leads to a lower bound. However, because only animals that die or are slaughtered can cause the spread of the disease to other cattle or exposure of humans to BSE-contaminated tissues, it is the

BSE prevalence among cattle that die or are slaughtered that is most relevant from a risk management perspective.

The remainder of this memo reviews alternative approaches for estimating BSE prevalence. The first approach depends on direct measurement of BSE in the component cattle sub-populations. We explain that high false positive rates in the normal sub-populations render this approach inefficient. The second approach focuses surveillance efforts on the high risk population and uses the estimated prevalence in this group to estimate the prevalence in the other groups.

1 Direct measurement of BSE prevalence in cattle sub-populations

This approach estimates BSE prevalence for the entire cattle population by adding the prevalence values for each group. The total number of BSE cases (n_{Total}) is $n_{HR} + n_A + n_J$, where the *HR* subscript refers to the population of “high risk” animals, the *A* subscript refers to normal adult animals, and the *J* subscript refers to normal juvenile animals. Table 1 defines these sub-populations based on the animal’s age and whether it displays clinical signs of disease.

Table 1
Cattle Sub-Population Definitions

	Age < 24 months	Age 24 to 29 months ^(a)	Age ≥ 30 months
No clinical signs	Normal Juvenile	Normal Juvenile	Normal Adult
Clinical Signs	Normal Juvenile	High Risk	High Risk

Notes:

- (a) We consider adults to include cattle at least 30 months of age. However, consistent with the definition of its targeted cattle population (USDA, 2004, p. 2), we assume animals with clinical signs that are at least 24 months of age are in the high risk sub-population.

Estimates for each of these components (\hat{x}_i) can be calculated as the product of the sample prevalence rate (\hat{r}_i), the number of animals in each population (N_i), and an adjustment for the false negative test detection rate ($\frac{1}{1 - FN_i}$). Hence, the total number of BSE cases can be estimated as

$$\hat{n}_{Total} = \sum_i \hat{r}_i \cdot N_i \cdot \frac{1}{1 - FN_i} \quad \text{Eq 1}$$

If we optimistically assume the false negative rate is zero, this approach and USDA’s proposed surveillance plan would be capable of detecting with 95% certainty a prevalence rate of 2.8×10^{-4} among the 6.2 million normal adult and high risk cattle that die each year (*i.e.*, 1,740 BSE cases). However, this interpretation of the data provides no insight regarding the prevalence rate among normal juveniles (see Table 2).

Table 2
95% Upper Confidence Limit on BSE Prevalence if no Animals Test Positive:
Estimates Based on Testing Only

Population	Number of Positive Detects	95% Upper Confidence Limit on $r^{(a)}$	Number of Animals Slaughtered per Year	Assumed BSE False Negative Rate	95% Upper Confidence Limit on n
HR	0 of 268,444	7.3×10^{-6}	446,000	0	3
A	0 of 10,000	3.0×10^{-4}	5,800,000	0	1,736
J	0 of 0	-	30,000,000	-	n_J
Total					1,739 + n_J

Notes:

(a) Estimated using Cannon and Roe (1982).

The sensitivity of this approach could in theory be substantially increased by testing the same proportion of animals in each sub-population. For example, testing approximately 4.4% of the high risk animals and 4.4% of the normal adults, *i.e.*, 20,000 high risk animals and 258,000 normal adults, would be capable of detecting a BSE prevalence of around 2×10^{-5} (132 positive animals among the 6.2 million normal adult and high risk cattle) with 95% certainty. However, this result depends on the assumption that the false negative rate is zero. It also continues to ignore the normal juvenile sub-population.

While the assumption of a zero false negative rate may be reasonable for full blown cases that would presumably belong to the high risk sub-population, this assumption is likely to be very optimistic for other cattle. After an animal is infected with BSE, definitive post mortem tests for the presence of the agent yield false negative results until not long before clinical signs develop. Although it is not known precisely when these tests become effective, a reasonable estimate is

three months prior to the development of clinical signs (personal communication, Lisa Ferguson, USDA APHIS, Veterinary Services, March 1, 2004).

We have estimated the false negative rates for normal adult and normal juvenile animals using a modified version of Harvard's BSE simulation model. This modified version of the model reports the characteristics of each BSE-positive animal that dies during the simulation. Characteristics reported include the animal's type (dairy, beef, beef reproductive), gender, age (months), months since the animal was infected with BSE, fraction of the incubation period elapsed at time of death, and death location (farm or slaughter facility). We assume that animals with BSE test negative if less than 90% of their incubation period has elapsed. We simulated the spread of BSE for 20 years following the introduction of contaminated feed (250 ID_{50s}) into the U.S.³ Our results indicate a false negative rate of 92% for normal adult cattle. For normal juvenile cattle, the false negative rate is 99.99%. Accounting for these false negative rates and the potential for BSE among normal juvenile animals suggests that the evaluating the surveillance data as described here is a relatively insensitive approach for detecting the presence of BSE in the U.S. cattle population.

Taking into account the false negative rates estimated in the previous paragraph (and continuing to ignore the normal juveniles for the moment) decreases the sensitivity of the "optimal" surveillance plan described earlier (20,000 high risk animals and 258,000 normal adults) so that only a BSE prevalence rate of 1.4×10^{-4} or greater can be detected.

2 Extrapolation of the BSE prevalence rate from the high risk sub-population to the normal sub-populations

The modeling approach described in this section uses empirical data or the Harvard BSE simulation to better characterize the relationship between BSE prevalence rates in different groups. In particular, we propose 1) estimating the number of BSE-positive animals in the high risk category using surveillance, and then 2) estimating the number of BSE-positive normal adults by scaling \hat{n}_{HR} by an estimate of the ratio of n_A to n_{HR} (designated $Q_{A:HR}$). Similarly, \hat{n}_J is estimated as $\hat{n}_{HR} \cdot Q_{J:HR}$. Hence, the total number of BSE-positive animals is estimated as

³ We simulated the introduction of contaminated feed, rather than the introduction of infected animals, because we did not want our results to be influenced by the characteristics of the animals introduced.

$$\hat{n}_{Total} = \hat{r}_{HR} \square N_{HR} \square \frac{1}{1 \square FN_{HR}} (1 + Q_{A:HR} + Q_{J:HR}). \quad \text{Eq 2}$$

We present two ways to estimate the values of $Q_{A:HR}$ and $Q_{J:HR}$. First, we can estimate these ratios using similar empirical values measured in other countries. In Switzerland, the BSE prevalence rate among fallen stock (FS) and emergency slaughter (ES) animals aggregated over the years 1999 and 2000 was approximately eight times greater than the BSE prevalence rate among routine slaughter animals. Recall that USDA's proposal to test approximately 268,000 high risk animals would be sufficiently powerful to establish that the prevalence rate is no more than 7.3×10^{-6} with 95% certainty. Assuming a zero false negative rate and applying the prevalence rate ratio of eight from the Swiss data, this result would imply a BSE prevalence rate of 9.1×10^{-7} among normal adult cattle ($7.3 \times 10^{-6} \div 8$). This rate corresponds to a total prevalence among normal adult cattle of approximately 5 BSE cases (5.8 million $\times 9.1 \times 10^{-7}$). The Swiss data do not provide any information on the BSE prevalence rate among juvenile cattle. Nor do they take into account the potential for a higher false negative rate among normal adult cattle than among high risk cattle. Finally, as noted earlier, differences in agricultural practices across countries make extrapolation of results from Switzerland to the U.S. uncertain.

An alternative approach for estimating $Q_{A:HR}$ and $Q_{J:HR}$ uses the modified version of Harvard's BSE simulation model described earlier in this memo. We again consider the characteristics of cattle infected with BSE at the time of their death following the introduction of 250 ID_{50s} into cattle feed. Table 3 summarizes the distribution of values for $Q_{A:HR}$ and $Q_{J:HR}$ based on 1,000 simulation runs. We provide two sets of distributions. The first set of distributions pertains to the total BSE prevalence rate – *i.e.*, including all animals infected with BSE even if laboratory testing would be incapable of detecting the presence of the disease. The second set of distributions pertains to the prevalence of detectable BSE only. It is the second set of distributions that is relevant for the purpose of comparing U.S. prevalence to other countries because other countries estimate only the rate of detectable BSE in their cattle populations.

Table 3
Summary Statistics for the BSE Prevalence Ratios

Fractile	Total BSE Prevalence		Prevalence Among Normal Adults and Juveniles of Detectable BSE Only	
	$Q_{A:HR}$	$Q_{J:HR}$	$Q_{A:HR}^{(a)}$	$Q_{J:HR}^{(b)}$
5 th	0.42	1.55	0.034	1.5×10^{-4}
10 th	0.50	1.82	0.040	1.8×10^{-4}
25 th	0.73	2.29	0.058	2.3×10^{-4}
50 th	1.00	3.00	0.080	3.0×10^{-4}
75 th	1.50	4.20	0.12	4.2×10^{-4}
90 th	2.25	6.25	0.18	6.3×10^{-4}
95 th	3.00	8.33	0.24	8.3×10^{-4}

Notes:

- (a) Assumes a false negative rate of 92%.
- (b) Assumes a false negative rate of 99.99%.

Estimating the total BSE prevalence

Using the median values from columns 2 and 3 of Table 3 in Equation 2, along with the assumption that the false negative rate is zero for BSE-positive cases in the high risk group, testing 268,000 animals from the high risk group would be capable of detecting a BSE prevalence () of around 16 with 95% certainty ($3.25 \times (1 + 1.0 + 3.0)$). Using the upper 95th percentile values for these ratios yields an upper bound for of around 40 ($3.25 \times (1 + 3.0 + 8.3)$). Because the total number of animals slaughtered in the U.S. each year is approximately 35 million, 40 animals corresponds to a prevalence rate one per one million cattle that die or are slaughtered. More refined bounds could be calculating by developing estimates for $Q_{A:HR}$ and $Q_{J:HR}$ using more realistic scenarios for the introduction of BSE into the U.S. and by establishing a more relevant time horizon for the simulation.

Estimating the prevalence of detectable BSE

Using the median ratios in columns 4 and 5 of Table 3 in Equation 2, testing 268,000 animals from the high risk group can detect a prevalence of approximately 3 with 95% certainty, a level that corresponds to a prevalence rate of approximately 1 per 10 million cattle that die or

are slaughtered. Even the upper bound estimates from columns 4 and 5 yield virtually the same result.

While the ratios in columns 4 and 5 of Table 3 are most appropriate for comparing the prevalence of BSE in the U.S. to the BSE prevalence in other countries, it is reasonable to ask what level of risk (to humans or other cattle) the non-detectable cases might pose. Using the simulation described earlier, we estimate that the average infectivity loads in normal juveniles and normal adults that have non-detectable BSE are approximately 120 and 130 cattle oral ID₅₀s, respectively. Because they are slaughtered at a young age, there are virtually no juveniles that reach the detectable stage of the disease. However, among normal adults that reach the detectable stage, the infectivity load is more than 20 times greater (average of 2,800 cattle oral ID₅₀s). Of course, the average infectivity load in animals that reach full clinical status is higher still, at 10,000 cattle oral ID₅₀s.

References

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