

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

**Evaluation of the Potential for Bovine Spongiform
Encephalopathy in the United States**

Joshua T. Cohen
Keith Duggar
George M. Gray
Silvia Kreindel

Harvard Center for Risk Analysis
Harvard School of Public Health

Hatim Abdelrahman
Tsegaye HabteMariam
David Oryang
Berhanu Tameru

Center for Computational Epidemiology
College of Veterinary Medicine
Tuskegee University

November 26, 2001
Revised October, 2003

31 **Acknowledgments**

32 This project benefited from information and advice from many individuals. Any errors or
33 misstatements are due to the authors, not the many contributors.

34
35 The authors gratefully acknowledge Alwynelle Ahl (USDA-ORACBA), Nathan E. Bauer
36 (USDA-FSIS), Paul Brown (NIH), Linda Detwiler (USDA-APHIS), David W. Harlan (Taylor
37 Byproducts, Inc), and Pedro Piccardo (Indiana University) for their scientific input and critical
38 review of different sections of the manuscript. We also thank Drs. H. Christopher Frey, John C.
39 Galland, Junyu Zheng, Bram E.C. Schreuder, and John Wilesmith who reviewed the original
40 report (November, 2001) for the USDA.

41
42 In addition we would like to thank the following individuals for providing scientific input and
43 support:

44
45 Gary Adams, Texas A&M University
46 John Adams, National Milk Producers Federation
47 Judd Aiken, University of Wisconsin-Madison
48 Steve Anderson, USDA-FSIS
49 Haluk Anil, Bristol University
50 David Asher, FDA
51 Harry Baker, Cambridge University
52 Mike Barry, Oklahoma City Zoo
53 Daniel Bohnenblust, Swiss Federal Statistical Office
54 Robin Bolin, ConAgra Beef Company
55 David Bolton, New York State Institute for Basic Research
56 Robert Brady, USDA-APHIS
57 Gerald R. Bratton, Texas A&M University
58 Robert Brewer, USDA-FSIS
59 Victoria Bridges, USDA-APHIS
60 Moira Bruce, Institute for Animal Health, Neuropathogenesis Unit, Edinburgh
61 Herbert Budka, University of Vienna
62 Terry Caviness, Caviness Packing Company
63 Richard Cawthorne, Ministry of Agriculture, Fisheries and Food, UK
64 Megna Chakrabarti, Harvard Center for Risk Analysis
65 Nguyen Chau, Harvard Center for Risk Analysis
66 Nick Chesnut, Union County Feedlot, New Mexico
67 Lily Chounlamountry, USDA-FSIS
68 John Clay, Dairy Records
69 Michelle Colby, Virginia-Maryland Regional College of Veterinary Medicine
70 Phillip Comer, DNV
71 Nancy Cook, Pet Food Institute
72 Maria Correa, North Carolina State University
73 Barbara Corso, USDA-APHIS
74 Ken Crandall, DHI-Provo
75 Randall Cutlip, USDA-Craig White, USDA-FSIS
76 Dyan Daly, National Food Center, Dublin
77 Dave Dargatz, USDA-APHIS
78 Arthur Davis, USDA, NVSL
79 Bryan Dierlam, American Cattlemen's Association

80 Marcus Doherr, BVET, Switzerland
81 Christl Donnelly, Oxford University
82 Basil Eastwood, USDA-CSREES
83 Dan Englejohn, USDA-FSIS
84 Lisa Ferguson, USDA-APHIS
85 Neil Ferguson, Oxford University
86 J. Fetrow, University of Minnesota
87 Lloyd Floyd, Kansas Dept. of Wildlife & Parks
88 Don Franco, National Renderers Association
89 Azra Ghani, Oxford University
90 Randy Gordon, National Grain & Feed Association
91 Daniel Gould, Colorado State University
92 George Graber, FDA
93 Temple Grandin, University of Illinois
94 John Gray, USDA-APHIS
95 Dicky Griffin, University of Nebraska
96 Scott Hafner, USDA-APHIS
97 Mark Hall, USDA-APHIS-NVLS
98 Rachael Hamilton, American Meat Science Association
99 J Hamir, USDA-ARS-NADC
100 Jeff Hansen, Murphy Farm Inc
101 Michael Hansen, Consumer's Union
102 David Harbour, Bristol University
103 Dagmar Heim, BVET, Office Veterinaire Federal, Switzerland
104 Jud Heinrichs, Penn State University
105 Christopher Helps, Bristol University
106 Peter Hewson, Ministry of Agriculture, Fisheries and Food, UK
107 Harold Hodges, BFD Corporation
108 Paul Honeyman, Ministry of Agriculture, Fisheries and Food, UK
109 John Honstead, FDA
110 Will Hueston, Virginia-Maryland Regional College of Veterinary Medicine
111 Nora Hunter, Institute for Animal Health, Neuropathogenesis Unit, Edinburgh
112 James Ironside, CJD Surveillance Unit, Edinburgh
113 Alan Jenny, USDA-APHIS, NVLS
114 Sherri Kochevar, ConAgra Beef Company
115 Chuck Lambert, American Cattlemen's Beef Association
116 John Lawrance, University of Iowa Extension Service
117 T. Lindley, TAMA
118 Ernest Justus Lücker, -Liebig University
119 Terry Lutz, USDA-AMS
120 Donna Malloy, USDA-APHIS
121 Jeronimo Mamaclay, USDA-FSIS
122 Jeffrey Martin, VLA Lasswade, Scotland
123 Danny Matthews, Ministry of Agriculture, Fisheries and Food, UK
124 Patrick McCaskey, USDA-FSIS
125 Dan McChesney, FDA
126 Janice Miller, USDA-ARS, NADC
127 Michael Miller, Colorado Division of Wildlife
128 Ray Millers, BFD Corporation
129 Burt Mitchel, FDA
130 Sarah Muirhead, Feedstuff Magazine

131 Dennis K. Mullane, Taylor By-Products, Inc
132 H.D. Norman, USDA-ARS
133 Greg Oliver, Australian Quarantine and Inspection Service
134 Arnold Paft, USDA-NAH
135 George Patrick, Taylor Packing Co. Inc
136 Alan Perna, United Cooperative Farmers Inc
137 Jody Pinter, AgSource Cooperative Services
138 Teresa Platt, Fur Commission USA
139 Ilpo Pölönen, Finnish Fur Breeders' Association
140 Burt Prichett, FDA
141 Jim Quigley, Animal Protein Corporation, Inc
142 Rosalind Ridley, Cambridge University
143 Elisa Rubi, Direccion General de Salud Animal, Mexico
144 R. Rubinstein, NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY
145 Larry Satter, USDA-ARS
146 Mary Jo Schmerr, USDA-ARS-NADC
147 Glen Schmidt, Colorado State University
148 Chuck Schuad, University of New Hampshire
149 Richard Sellers, American Feed Industry Association
150 Craig Shultz, USDA-FSIS
151 Bill Smith, USDA-APHIS
152 L. Smith, National Nutrition Program Advisor, USDA
153 Charlie Sniffen, Miner Institute
154 Walt Solonynka, Conagra Beef Company
155 Robert Somerville, Institute for Animal Health, Neuropathogenesis Unit, Edinburgh
156 John Spouge, DNV
157 Richard Theise, International Natural Casing Association
158 David Thomas, Extension Sheep Specialist, Madison, WI
159 Judy Thompson, Canadian Food Inspection Agency
160 Chris Toyne, Agriculture and Fisheries Branch, ABARE, Australia.
161 Donald Upton, United Cooperative Farmers Inc
162 Andrea Vicari, North Carolina State University
163 James Voss, Colorado State University
164 Paul Walker, Illinois State University
165 Gary Weber, National Cattlemen's Beef Association
166 Gerald Wells, Central Veterinary Laboratory, UK
167 Marion Weybridge, Ministry of Agriculture, Fisheries and Food, UK
168 Craig White, USDA-FSIS
169 John Wilesmith, Central Veterinary Laboratory, UK
170 Jim Wilkus, USDA-FSIS
171 Robert Will, CJD Surveillance Unit, Edinburgh
172 Elizabeth Williams, University of Wyoming
173

Table of Contents

175	Acknowledgments	i
176	Executive Summary	vii
177	1 Introduction	1
178	2 Background	4
179	2.1 Overview of Transmissible Spongiform Encephalopathies (TSEs)	4
180	2.1.1 Transmissibility	6
181	2.1.2 The Species Barrier	8
182	2.1.3 Susceptibility	9
183	2.2 The Origin of the BSE Epidemic in the UK	14
184	2.2.1 Scrapie in Sheep	14
185	2.2.2 Infrequent Sporadic BSE	16
186	2.2.3 Toxic Agents and Other Hypotheses	17
187	2.2.3.1 Organophosphate (OP) Pesticides	17
188	2.2.3.2 Copper Deficiency	18
189	2.2.3.3 Heavy Metal Exposure	18
190	2.2.3.4 Autoimmune Disease	19
191	2.2.3.5 Use of Pituitary Hormones	19
192	2.2.3.6 Wild African Antelope	20
193	2.3 Sources of BSE Infectivity	20
194	2.3.1 Spontaneous BSE	20
195	2.3.2 Import of BSE Infectivity into the United States	22
196	2.3.2.1 Imported Live Cattle from the UK	22
197	2.3.2.2 Imported Cattle from Continental Europe	22
198	2.3.2.3 Imported Cattle from Non-European Countries	23
199	2.3.2.4 Imported MBM and Feed	23
200	2.3.3 Domestic Scrapie	24
201	2.3.4 Chronic Wasting Disease: Oral Exposure	25
202	2.3.5 Chronic Wasting Disease: Lateral Transmission	27
203	2.3.6 Mink	27
204	2.3.7 Pigs	28
205	2.3.7.1 Potential Infectivity in Pigs due to TSE Infection	29
206	2.3.7.2 Potential Infectivity in Materials Consumed by Pigs	31
207	2.3.8 Poultry	32
208	2.3.9 Recycled Products	32
209	2.3.9.1 Plate Waste	33
210	2.3.9.2 Gelatin	34
211	2.3.9.3 Milk	34
212	2.3.9.4 Blood and blood products	35
213	2.3.9.5 Tallow	35
214	2.4 Measures Taken to Protect Against BSE	36
215	2.4.1 General Issues Related to the Surveillance of BSE and the Deactivation of the BSE Agent	36
216	2.4.2 Actions to Address BSE in the UK	38
218	2.4.3 Actions to Address BSE in Europe	40
219	2.4.4 Measures to Prevent the Establishment of BSE in the United States Cattle Population ..	41
220	2.4.5 BSE Surveillance in the United States	45
221	3 Methodology	47
222	3.1 Simulation Model and Base Case Assumptions	47
223	3.1.1 Cattle Population Dynamics	48
224	3.1.1.1 Size of Cattle Population, Birth Rates, Slaughter Rates, and Rates of Death due to Other ..	49
225	3.1.1.2 Causes	49
226	3.1.1.2 Proportion of Animals That Die on Farm that Are Rendered	51
227	3.1.1.3 Cattle Consumption of Bypass protein and Blood Meal	51
228	3.1.1.4 BSE Dose-Response	51

229	3.1.1.5	Maternal Transmission	52
230	3.1.1.6	BSE Incubation Period, and Time Until Death Following Onset of Clinical Signs.....	52
231	3.1.2	The Slaughter Process.....	53
232	3.1.2.1	Level of Infectivity and Distribution of Infectivity Throughout the Carcass.....	53
233	3.1.2.2	<i>Antemortem</i> Inspection	55
234	3.1.2.3	Stunning.....	56
235	3.1.2.4	Exsanguination	57
236	3.1.2.5	Disposition of Brain.....	58
237	3.1.2.6	Splitting and Aerosolization	58
238	3.1.2.7	Disposition of the Spinal Cord and Dorsal Root Ganglia	58
239	3.1.2.8	Postmortem Inspection	61
240	3.1.2.9	Recovery of Material for Potential Human Consumption	61
241	3.1.3	Rendering and Feed Production.....	62
242	3.1.3.1	Rendering Inactivation.....	62
243	3.1.3.2	Meat and Bone Meal Production	63
244	3.1.3.3	Feed Production.....	64
245	3.1.3.4	On Farm Feeding	66
246	3.1.4	Potential Human Exposure	66
247	3.2	Impact of Alternative Assumptions on Cattle Infected and Human BSE Exposure	68
248	3.2.1	Cattle Population Dynamics	71
249	3.2.1.1	Size of Cattle Population, Birth Rates, Slaughter Rates, and Rates of Death Due to Other Causes.....	71
250			
251	3.2.1.2	Proportion of Animals That Die on Farm That Are Rendered.....	72
252	3.2.1.3	Cattle Consumption of Bypass Protein and Blood Meal	72
253	3.2.1.4	BSE Dose Response	73
254	3.2.1.5	Maternal Transmission	73
255	3.2.1.6	BSE Incubation Period, and Time Until Death Following Onset of Clinical Signs.	74
256	3.2.2	The Slaughter Process.....	75
257	3.2.2.1	Level of Infectivity and Distribution of Infectivity Throughout the Carcass.....	75
258	3.2.2.2	<i>Antemortem</i> Inspection	76
259	3.2.2.3	Stunning.....	76
260	3.2.2.4	Exsanguination	76
261	3.2.2.5	Disposition of Tissues and Potential for Human Exposure	76
262	3.2.2.6	Splitting and Aerosolization	77
263	3.2.2.7	Disposition of the Spinal Cord and Dorsal Route Ganglia	77
264	3.2.2.8	Postmortem Inspection	78
265	3.2.2.9	Recovery of Material for Potential Human Consumption	78
266	3.2.3	Rendering and Feed Production.....	79
267	3.2.4	Potential Human Exposure	79
268	3.2.5	Simultaneous Evaluation of Multiple Worst Case Assumptions	80
269	3.2.6	Summary.....	80
270	3.3	The Base Case: Impact of Alternative Sources of Infectivity.....	82
271	3.3.1	Spontaneous BSE.....	83
272	3.3.2	Import of Infected Cattle or Contaminated Cattle Feed.....	84
273	3.3.3	Domestic Scrapie	85
274	3.3.4	Chronic Wasting Disease: Oral Exposure.....	87
275	3.3.5	Chronic Wasting Disease: Lateral Transmission	89
276	3.3.6	Mink.....	89
277	3.3.7	Pigs	90
278	3.3.8	Poultry.....	90
279	3.3.9	Recycled Waste.....	90
280	3.4	Alternative Scenarios Evaluated Using the Simulation Model	91
281	3.4.1	Switzerland	91
282	3.4.2	Spontaneous Disease as a Potential Source of Infectivity in the U.S.....	94
283	3.4.3	Cattle Imported into the U.S from the UK During the 1980s	94
284	3.4.4	Risk Management: Specified Risk Materials (SRM) Ban.	96

285	3.4.5	Risk Management: A Ban on Rendering Animals that Die on the Farm	96
286	4	Results	97
287	4.1	Base Case	99
288	4.2	Sensitivity Analyses.....	100
289	4.2.1	Number of Additional Infected Cattle	100
290	4.2.2	Infectivity in Food Available for Human Consumption	103
291	4.3	Alternative Sources of Infectivity	103
292	4.3.1	Spontaneous BSE.....	104
293	4.3.2	Imports.....	104
294	4.3.3	Scrapie	105
295	4.4	Alternative Scenarios	106
296	4.4.1	Switzerland	106
297	4.4.2	Spontaneous With no Feed Ban.....	107
298	4.4.3	Cattle Imported from the UK in the 1980s.....	108
299	4.4.4	Specified Risk Material Ban.....	110
300	4.4.5	Prohibition on Rendering Animals that Die on the Farm.....	111
301	4.5	Summary	111
302		Glossary.....	116
303		References.....	120
304			
305		Appendix 1	
306		Appendix 2	
307		Appendix 3 Model Output	
308		Appendix 3A Tables	
309		Appendix 3B Graphs	
310		Appendix 3C Description of Model Output Tables (Appendix 3A) and Graphs (Appendix 3B)	
311		Appendix 3D Summary of Worst Case Sensitivity Analysis Results by Output Statistic	
312		Appendix 4 Estimating Numerical Stability for Simulation Statistics	
313		Appendix 5 Number of Cattle Oral ID _{50s} Imported from the UK Before the Import Ban	
314			

315 **Executive Summary**

316 In 1998 the United States Department of Agriculture asked the Harvard Center for Risk
317 Analysis to evaluate the robustness of U.S. measures to prevent the spread of bovine spongiform
318 encephalopathy (BSE or “mad cow disease”) to animals and humans if it were to arise in this
319 country. BSE is a member of a family of diseases that includes scrapie in sheep and goats,
320 chronic wasting disease in certain North American deer and elk, transmissible mink
321 encephalopathy, and the human ailments Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob
322 disease, and Kuru.

323

324 We have developed a probabilistic simulation model to help characterize the
325 consequences of introducing BSE into the U.S. *via* various means. Our model allows us to
326 predict, for example, the number of newly infected animals that would result from introduction of
327 BSE, the time course of the disease following its introduction, and the potential for human
328 exposure to infectious tissues. We evaluate key processes and procedures that make the spread of
329 disease more or less likely. Results are presented as distributions reflecting the probabilistic
330 nature of the model and the processes simulated.

331

332 Our analysis finds that the U.S. is highly resistant to any introduction of BSE or a similar
333 disease. BSE is extremely unlikely to become established in the U.S. For example, in a
334 hypothetical scenario in which ten cattle infected with BSE are imported into the U.S., on average
335 only four new cases of BSE would occur. Moreover, the disease is virtually certain to be
336 eliminated from the country within 20 years after its introduction. These results assume that the
337 conditions affecting the spread of BSE in the U.S. would remain unchanged for the 20 years
338 following its introduction. The new cases of BSE would result primarily from lack of compliance
339 with the regulations enacted to protect animal feed. The import of one infected animal yields on
340 average less than one new BSE case in 20 years and the disease is likely to be quickly eliminated
341 from the U.S. following its introduction. Likewise, there appears to be no potential for an
342 epidemic of BSE resulting from scrapie, chronic wasting disease, or other cross-species
343 transmission of similar diseases found in the U.S. Even if they existed, these hypothetical sources
344 of BSE could give rise to only around two cases per year. Similarly, if the disease does indeed
345 occur spontaneously in cattle, as some have suggested, it would result in one to two cases per
346 year with little spread.

347

348 Only a small amount of potentially BSE-contaminated tissues would reach the human
349 food supply and be available for possible human consumption. We express the amount of
350 infectivity in terms of cattle oral ID₅₀s for the purpose of quantifying both animal and human
351 exposure to this agent. A cattle oral ID₅₀ is the amount of infectious tissue that would, on
352 average, cause 50% of exposed cattle to develop BSE. The relationship between human exposure
353 quantified in terms of cattle oral ID₅₀s and likelihood of human disease is unknown, but European
354 authorities suggest that the cattle disease may be 10 to 100,000 times less virulent in humans
355 (European Union Scientific Steering Committee 1999a; European Union Scientific Steering
356 Committee 2000a). In the entire 20 year period following the import of ten BSE-infected cattle,
357 the mean estimate for the amount of infectivity potentially available for human exposure is 39
358 cattle oral ID₅₀s. The greatest sources of infectivity include consumption of cattle brain, spinal
359 cord, and meat derived from advanced meat recovery systems. Some potential exposure would
360 result from the presence of spinal cord in certain bone-in cuts of beef, like T-bone steaks, and
361 consumption of cattle intestines. Potential human exposure resulting from spontaneous disease or
362 cross-species transmission of scrapie is predicted on average to be no more than 100 cattle oral
363 ID₅₀s over 20 years.

364
365 Even in an extreme case, which we characterize using the 95th percentile of the output
366 distribution from the simulation, the import of ten infected animals leads to only 16 new cases of
367 BSE over twenty years. The 95th percentile value for potential human exposure is 180 cattle oral
368 ID₅₀s over 20 years, nearly five times the mean value. These predictions can be compared with
369 the experience in the United Kingdom, where it is estimated that there were nearly one million
370 infected animals and it is likely millions of cattle oral ID₅₀s available for potential human
371 exposure.

372
373 Measures in the U.S. that are most effective at reducing the spread of BSE include the
374 ban on the import of live ruminants and ruminant meat and bone meal from the UK (since 1989)
375 and all of Europe (since 1997) by USDA/APHIS, and the feed ban instituted by the Food and
376 Drug Administration (FDA) in 1997 to prevent recycling of potentially infectious cattle tissues.
377 This feed ban greatly reduces the chance that BSE will spread from an infected animal back to
378 other cattle through feed. Our model reflects incomplete compliance with the FDA feed ban and
379 we evaluate the potential risks resulting from exceptions to the ban. Measures instituted in meat
380 packing plants by the industry and the USDA Food Safety Inspection Service (FSIS) have
381 reduced the opportunity for infectious tissues to contaminate human food.

382

383 Specific pathways or practices that would contribute the most to the spread of BSE if it
384 were introduced into the U.S. relate to compliance with the FDA feed ban and include misfeeding
385 on the farm (*i.e.*, administration to cattle of feed labeled as prohibited for that purpose) and the
386 mislabeling of feed and feed products prohibited for consumption by cattle. The disposition of
387 cattle that die on the farm would also have a substantial influence on the spread of BSE if this
388 disease were introduced into the U.S. Factors that influence potential human exposure include
389 the handling of brain and spinal cord in processing plants and how well inspectors would detect
390 animals with BSE at slaughter.

391

392 Our model is not amenable to formal validation because there have been no controlled
393 experiments in which the consequences of introducing BSE into a country has been monitored
394 and measured. However, as a test of the model's plausibility, we modeled the small BSE
395 outbreak identified in Switzerland following the introduction of BSE infectivity from the UK.
396 Working with experts in Switzerland, we identified appropriate values for model parameters
397 necessary to appropriately characterize that country's practices and procedures and then
398 simulated the introduction of BSE infectivity. Our simulation took into account risk management
399 actions, such as feed bans instituted by the Swiss. The model's predictions were reasonably close
400 to empirical observations. For example, the model predicted that during the Swiss outbreak, there
401 would have been 230 animals that developed clinical signs of disease. To date, the Swiss have
402 detected 398 animals with BSE. The time course of the outbreak predicted by the model also
403 reasonably resembled the pattern observed in Switzerland. The ability of the model to reasonably
404 replicate the magnitude and time course of the Swiss outbreak gives some confidence in the
405 structure of our model, especially in light of the many unknown factors associated with this
406 episode. In fact, modest revision of highly uncertain assumptions from our "first guess" values,
407 based on advice from personnel from the Swiss Federal Veterinary Office, yielded results that
408 were even more consistent with observed data.

409

410 We also evaluated the potential for BSE to have entered the U.S. prior to the 1989 ban on
411 the import of UK cattle. BSE has not been detected in the U.S. despite 12 years of active
412 surveillance of high-risk animals. Yet several groups, including the European Union in their
413 Geographically Based Risk Assessment of the U.S. (European Union Scientific Steering
414 Committee 2000d), have highlighted the 334 animals brought into the U.S. from the UK between
415 1980 and 1989. These animals were imported as breeding stock, not as beef or dairy production

416 animals. This fact is likely to have reduced their potential for exposure to BSE before their
417 export from the UK. In addition, none of these animals came from a farm on which there was a
418 case of BSE in animals from the same birth cohort (same birth farm and year). Many came into
419 the U.S. before BSE was even a recognized disease (the first case was confirmed in the UK in
420 1986). The USDA has identified and traced the disposition of these animals and has verified that
421 161 were disposed of in a manner that poses no risk to other animals or to humans. However, the
422 Department has not been able to conclusively make this determination for the remaining 173
423 animals. Using data identifying the year of birth, the year of import, the date of the animal's last
424 known sighting, and information characterizing the time course of the disease following infection,
425 we have estimated the amount of BSE infectivity that could have theoretically been introduced
426 into the U.S. from these 173 animals. We then used this estimate in our model to predict the
427 possible consequences in the U.S.

428

429 Our analysis concludes that there is more than an 80% chance that the import of these
430 animals resulted in no exposure of U.S. cattle to BSE infectivity. Even if U.S. animals were
431 exposed to BSE, there is a significant chance that the exposure resulted in no new cases of
432 disease. Our analysis indicates that there is only a small chance that BSE spread to U.S. cattle but
433 that the number of cases was sufficiently small to avoid detection by U.S. government
434 surveillance. The analysis also shows that if these imports did introduce BSE into the U.S.,
435 measures taken by the government and industry since 1997 will have arrested the disease and
436 begun to eradicate it.

437

438 Our evaluation of potential risk mitigation actions highlights potential measures to further
439 reduce the already low likelihood that if BSE were introduced into the U.S., it could spread to
440 cattle or contaminate human food. Prohibiting the rendering of animals that die, potentially from
441 BSE, prior to being sent to slaughter (*i.e.*, animals that "die on the farm") substantially reduces
442 the potential for contamination of cattle feed, decreasing the average predicted additional cases of
443 BSE following introduction of ten infected cattle by more than 80%. Implementation of a UK-
444 style ban on specified risk material (*e.g.*, spinal cords, brains, vertebral columns) from both
445 human food and animal feed reduces the predicted number of additional BSE cases in cattle by
446 almost 90% and potential human exposure by 95%. These findings serve to illustrate the types of
447 evaluations of alternative risk management strategies that can be conducted using the model.

448

Executive Summary

449 In summary, measures taken by the U.S. government and industry make the U.S. robust
450 against the spread of BSE to animals or humans should it be introduced into this country.
451 Preventing infected animals or contaminated feed from entering the country, ensuring compliance
452 with the FDA feed ban, and reducing the potential for contaminated tissues to enter the animal
453 feed or human food supply will ensure that these risks remain low. If BSE has been introduced
454 into the U.S., as has been suggested by some observers, the course of the disease has been
455 arrested and it is destined for eradication by the measures currently in place.
456

457 **1 Introduction**

458 Bovine spongiform encephalopathy (BSE) is a disease of cattle that was first documented
459 in the United Kingdom in 1986. It has since spread to several countries in Europe, and most
460 recently to Japan. The disease causes the degeneration of central nervous system (CNS) function,
461 ultimately leading to death in all cases. Perhaps more worrisome is the possibility that meat
462 products contaminated with BSE infectivity¹ can cause a human form of this illness, known as
463 variant Creutzfeldt-Jakob Disease, or vCJD. Like BSE, vCJD causes CNS degeneration and is
464 always fatal. Unlike many other animal-borne diseases, the agent thought to be responsible for
465 BSE and possibly vCJD is at least partially resistant to destruction by standard cooking practices,
466 sterilization procedures, and processes used to recycle bovine protein prior to its use as a feed
467 supplement. For that reason, the presence of BSE can lead to the spread of disease among other
468 animals, and potential health risks for people.

469

470 Although there has never been a case of BSE documented in the United States, the
471 potential for the disease to spread, and the potential threat it poses to people has raised concern in
472 this country. In order to better characterize the nature of these risks, the United States
473 Department of Agriculture (USDA) commissioned the Harvard Center for Risk Analysis to
474 conduct a study of BSE in the U.S.

475

476 This study was undertaken to investigate potential pathways by which BSE or other TSEs
477 could arise in the United States (U.S.) cattle population². In particular, the analysis describes the
478 use of a quantitative simulation model that characterizes how the introduction of BSE would
479 affect animal health over time, and the extent to which it could result in human exposure to
480 contaminated food products. The ability of this model to quantify various aspects of the disease's
481 progression (*e.g.*, number of animals infected over time, quantity of the transmissible agent in
482 food presented for human consumption) distinguishes it from other efforts to characterize BSE
483 risk, such as the European Union's Scientific Steering Committee report on the Geographical
484 Risk of Bovine Spongiform Encephalopathy (European Union Scientific Steering Committee

¹ Although the exact etiology of BSE is uncertain, in many respects the transmission of the disease can be evaluated as though it arises from an infectious agent. Because the nature of the agent is still a matter of some scientific debate, we use the term "infectivity" to characterize materials that can transmit the disease from one animal to another or potentially from animals to people.

² For the purpose of the study, "other TSEs" are defined to be naturally occurring animal prion diseases that if present in cattle, will manifest with clinical and histopathological characteristics that are similar to those

485 2000c). We have used the simulation model to determine the impact of possible past
486 introductions of BSE into the U.S., to identify those risk management control options that most
487 influence the spread of disease, and to identify those sources of uncertainty that have the greatest
488 impact on our results. This information can be used to help identify the most promising control
489 measures and to prioritize data collection and research efforts.

490

491 A key goal of this analysis is to determine whether BSE would develop into a self-
492 sustaining epidemic if it were introduced into the U.S., or if its prevalence would tend to decrease
493 over time, leading eventually to its eradication. Which of these two possibilities occurs depends
494 on the average number of new cases of disease that result from each existing case. This value,
495 designated R_0 , is referred to as the epidemic's basic reproduction rate (Anderson 1991). If R_0
496 exceeds unity, the disease will tend to spread. On the other hand, if R_0 is less than unity, the
497 number of cases will tend to decline over time, and ultimately the disease will die out. Assuming
498 that an initial introduction of BSE into the U.S. is limited in magnitude, the ultimate impact of the
499 introduction will depend vitally on whether R_0 exceeds unity. This concept corresponds to the
500 issue of "stability" that is a focus of the European Union's approach to geographic BSE
501 assessments (European Union Scientific Steering Committee 2000c; European Union Scientific
502 Steering Committee 2000d).

503

504 The analysis is not a complete human health risk assessment in two respects. First, we do
505 not quantify the probability that BSE will be introduced into the U.S. Hence, all our risk
506 estimates are conditional on hypothetical scenarios. Second, although we quantify potential
507 human exposure to BSE-contaminated food products, we do not estimate how many people will
508 contract variant Creutzfeldt-Jakob Disease (vCJD). We have omitted quantitative treatment of
509 both of these issues because the available information is inadequate.

510

511 The remainder of this study is organized as follows. Section 2 first describes the different
512 types of TSEs, their characteristics, theories as to the origin of the BSE epidemic in the UK, and
513 measures taken to control the spread of BSE. Next, Section 2 discusses the pathways for the
514 introduction of disease in further detail, including the potential for spontaneous development of
515 BSE, transmission from another species in the U.S. with a prion disease, the import of BSE-
516 infected cattle, or use of cattle rations that may contain contaminated material. Section 3

associated with cattle BSE. For the remainder of this document, the term "BSE" will collectively refer to BSE and to these other TSEs.

Section 1

517 describes our methodology, including the simulation model used in this analysis and the specific
518 scenarios evaluated. Section 4 summarizes our results, and concludes with a discussion of our
519 findings.
520

521 **2 Background**

522 This section provides background for the analysis described in this report. Section 2.1
523 outlines the characteristics of transmissible spongiform encephalopathies (TSEs), the class of
524 diseases to which BSE belongs. Section 2.2 reviews the hypotheses advanced for the origin of
525 the BSE epidemic in the UK. Section 2.3 describes potential pathways by which BSE could be
526 introduced into the U.S. Finally, Section 4 reviews regulatory actions taken by governments
527 around the world to slow the spread of this disease.

528

529 **2.1 Overview of Transmissible Spongiform Encephalopathies (TSEs)**

530 Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a
531 family of rare, slowly progressive, and uniformly fatal neurodegenerative disorders that affect
532 humans and animals. All of these diseases have incubation periods of months to years between
533 infection and the onset of clinical signs. The prevailing hypothesis is that these diseases are
534 caused by novel agents called prions. In humans, prion diseases may present as genetic,
535 infectious, or sporadic disorders, and all involve the modification of the prion protein. Known
536 TSEs include:

537

- 538 • Creutzfeldt-Jakob disease (CJD), Kuru, Gerstmann-Straüssler-Scheinker (GSS),
539 and Fatal Familial Insomnia (FFI) in humans;
- 540 • Scrapie in sheep and goats;
- 541 • Transmissible Mink Encephalopathy (TME) in mink;
- 542 • Chronic Wasting Disease (CWD) of deer and elk; and
- 543 • Bovine Spongiform Encephalopathy (BSE) in cattle.

544

545 TSEs have also been observed in exotic cats and ungulates in zoo collections. The source of
546 infection is not known. Other examples, such as Feline Spongiform Encephalopathy (FSE), are
547 thought to be the result of cross-species transmission of a TSE (BSE in the case of FSE). Variant
548 CJD (vCJD) is a newly discovered TSE of humans and is likely the result of exposure to the BSE
549 agent.

550

551 The first records of TSEs date back to the early 18th century (Stockman 1913; Brown
552 1998b), with the mention of scrapie in sheep. The name of the disease reflects its associated
553 clinical signs, including the tendency of the sheep to scrape off their wool on fences or other
554 objects. Experimental transmission of scrapie to other species, such as mice and goats,
555 demonstrated that the disease was transmissible and had a very long incubation period (Cullie
556 1936; Cullie 1939; Pattison 1959).

557

558 During the 1950s, many scientists became interested in Kuru, a fatal disease that affected
559 the Fore population of Papua, New Guinea. Kuru is characterized by neurologic signs and
560 neuropathologic changes similar to those of scrapie although it has other signs (e.g., myoclonus)
561 not seen in scrapie but found in other TSEs (Klatzo 1957; Zigas 1957; Alpers 1970). These
562 similarities were pointed out by Hadlow in 1959, who suggested that Kuru also might be
563 transmissible to other animals (Hadlow 1959). Subsequently, Gajdusek and his colleagues
564 succeeded in transmitting Kuru to chimpanzees (Gajdusek 1966). This experiment supported the
565 hypothesis that Kuru is transmitted by an infectious mechanism (*i.e.*, ritualistic cannibalism).
566 Later, other spongiform encephalopathies were found to be transmissible, including CJD, FFI,
567 TME, CWD, and BSE. To date, most of the experimental data on TSEs comes from studies of
568 CJD and scrapie. More recently, BSE has become an area of active research.

569

570 The specific agent responsible for TSE diseases has not been identified with certainty, but
571 the leading theory suggests that the etiologic agent is an abnormally configured protein normally
572 encoded by the host (prion protein or PrP) (Bolton 1982; Prusiner 1982; Prusiner 1994; Prusiner
573 1998). Normal prion protein (PrP^c) is soluble in detergents and has a predominantly α -helical
574 structure. In contrast, abnormal PrP (PrP^{sc}) is insoluble in detergents, relatively resistant to
575 proteases, and has a predominantly β -sheet secondary structure. Although still a matter of
576 controversy, PrP^{sc} appears to accumulate in an infected host and eventually cause disease (Hsiao
577 1991; Bueler 1993; Telling 1995; Manson 1999; Hill 2000). Deposits of PrP^{sc} in tissues are
578 associated with the presence of transmissible infectivity (McKinley 1983). Additionally, PrP^{sc} is
579 the only molecular marker specific for TSE infections. Spongiform degeneration, neuronal
580 vacuolation, and gliosis appear to be associated with abnormal PrP deposition. Remarkably, TSE
581 infection has been reported in the absence of detectable PrP^{sc} (Lasmezaz 1997) and PrP^{sc} formed
582 *in vitro*, by conversion of PrP^c, has not yet produced disease in animal bioassays (Hill 1999). The
583 etiologic agent is not inactivated by treatments that usually destroy bacteria and viruses

584 (Kimberlin 1983; Taylor 1991a; Taylor 1991b; Taylor 1993). No immune response to the agent
585 has been detected.

586

587 An alternative hypothesis to the prion theory, referred to as the virino model, proposes
588 that the agent consists of a small nucleic acid that acts as an informational molecule, and that this
589 molecule is protected by the host PrP (Dickinson 1988). Despite several attempts (Borras 1986;
590 Duguid 1988), no exogenous nucleic acid has been identified in experimental TSE. The virino
591 model suggests different genetic “strains” of the agent are responsible for the phenotypic
592 variability in the disease. The protein only (prion) hypothesis proposes that conformational
593 isoforms of PrP are responsible for such variability. Another theory proposes that TSEs are
594 caused by conventional viruses (Diringer 1994; Manuelidis 1995). However, no infection-
595 specific nucleic acid has yet been detected.

596

597 The mechanisms by which infection occurs for most naturally occurring TSEs are
598 uncertain. Different animal TSEs appear to be passed in part by lateral transmission and perhaps
599 by maternal transmission to offspring in natural settings. The human spongiform
600 encephalopathies are considered to be either sporadic, inherited, or acquired by an infectious
601 mechanism (Masters 1978; Hsiao 1990; Brown 1994a; Will 1996; McLean 1998). Finally, there
602 is evidence that for some TSE diseases, susceptibility has a genetic component (Poulter 1992;
603 Carlson 1994; Goldmann 1996; Hunter 1996; Bossers 1997; Hunter 1997a; Hunter 1997b).

604

605 The remainder of Section 2.1 has three parts. Section 2.1.1 discusses the means by which
606 TSEs are passed from one animal to another, and perhaps from animals to humans. Section 2.1.2
607 introduces the concept of the “species barrier,” a phenomenon that makes passage of a TSE from
608 one species to another far less “efficient” (and hence less likely) than passage between animals of
609 the same species. Finally, Section 2.1.3 discusses susceptibility, *i.e.*, the tendency for some
610 animals to be more likely than others to become infected following exposure to the infective
611 agent.

612

613 **2.1.1 Transmissibility**

614 TSE diseases can be passed from an infected individual to others under only certain
615 conditions. While the potential for natural transmission has been demonstrated only for some
616 TSEs, transmission in an experimental setting has been demonstrated for most.

617

618 Transmission of a TSE disease from one human to another appears to be limited to cases
619 of “iatrogenic transmission,” associated with surgery, use of cadaveric hormones, and ritualistic
620 cannibalism. Iatrogenic transmission is the only known route of transmission for CJD.

621 Documented cases have involved the use of contaminated silver electrodes used for stereotactic
622 electroencephalography, the use of contaminated neurosurgical instruments (Collinge 1997), and
623 the use of contaminated tissues in transplant procedures (cornea, dura mater). The use of
624 contaminated hormones preparations (growth hormone or gonadotropin prepared from cadaveric
625 pituitary glands) has been linked to transmission of TSEs in humans. Kuru has been transmitted
626 from person to person as the result of ritualistic cannibalism in the people of Papua, New Guinea.
627 In this case, the most likely route of exposure was *via* ingestion, although transdermal or mucous
628 membrane exposure cannot be ruled out.

629

630 Transmission of TSE diseases from one animal to another of the same species in the
631 absence of experimental intervention has been extensively documented in the case of sheep-borne
632 scrapie (Hadlow 1982). The mechanism by which other sheep in the same flock become infected
633 appears to be associated with exposure to infected placenta (Race 1998b), although other routes
634 of exposure may also play a role in transmission. In sheep, transmission has also been linked to
635 the use of vaccines (Gordon 1939; Gordon 1946; Gordon 1959; Agrimi 1999), although the
636 relationship is not conclusive. Natural transmission has also been identified in CWD (Williams
637 1982). In the case of CWD, it has been postulated that transmission is caused by pasturing on
638 ground occupied by infected animals (Miller 1998). Presumably, some long-lived agent in the
639 environment can pass the disease between individuals (Sigurdson 1991; Skarphedinsson 1994).
640 Naturally occurring mutations capable of causing the disease have not been identified in animals
641 (Chesebro 1999).

642

643 Several species and animal breeds have been used as experimental models for TSEs,
644 including mice, hamsters, and non-human primates. Results from these experiments indicate that
645 natural (oral) transmission is substantially less efficient than transmission *via* intracerebral (i.c.)
646 injection, the procedure usually used for transmission in experimental models. For example, in
647 the case of BSE, transmission *via* oral ingestion is as much as 100,000 times less efficient than
648 i.c. injection (for a review of the literature, see (European Union Scientific Steering Committee
649 2000a)). Experimental data using a TSE mouse model indicate that intravenous injection
650 produces disease five to seven times less efficiently than i.c. injection (Brown 1999). Finally,

651 intra-peritoneal (i.p.) administration of infectivity is estimated to be 100 times less efficient than
652 i.c. transmission (Kimberlin 1988).

653

654 2.1.2 The Species Barrier

655 Interspecies transmission of TSEs is mitigated by a so called “species barrier”. This
656 barrier represents the decreased efficiency with which TSEs are passed from one animal to a
657 second animal of a different species, compared with the efficiency with which the TSE is passed
658 among animals of the same species. That is, a much greater amount of infective material is
659 necessary to infect an animal from a different species than is needed to pass the disease to an
660 animal of the same species. The species barrier also is associated with an increase in the
661 disease’s incubation period (*i.e.*, the delay between exposure to the agent resulting in infection
662 and the manifestation of disease). In some instances the species barrier seems to confer complete
663 resistance to transmission. It is at least conceptually possible that an animal failing to develop the
664 disease following cross species challenge would become infected if administered a sufficiently
665 large dose of infectivity, or would manifest clinical signs of disease if it somehow lived longer
666 than the incubation period associated with the species barrier (Hill 2000).

667

668 Although transmission of a TSE from one species to another may be less efficient than
669 the transmission within the same species, once it occurs, the TSE may become “adapted” to the
670 new host. Because it has adapted to the new species, it can be transmitted (at least
671 experimentally) more efficiently among members of that species, and the incubation period
672 becomes shorter and less variable. For example, when scrapie is transmitted experimentally from
673 one species to another, the incubation period is usually longer in the first passage than in
674 subsequent passages within the new species (Dickinson 1976).

675

676 The species barrier probably reflects some combination of factors including differences
677 between the donor’s and recipient PrP. Scrapie studies conducted in mice, rats, and hamsters
678 demonstrate the presence of a species barrier. These findings include pathogenesis differences
679 between the first and subsequent passages in the new species, and how rapidly the transmitted
680 strain replicates in the new host (Kimberlin 1987; Kimberlin 1989), and others.

681

682 The response of some TSEs exhibits heterogeneity within a species, a characteristic that
683 appears to be due to the existence of different strains of the agent. Strains are distinguished by

684 highly replicable differences in the incubation period, neuropathology, and host range (Fraser
685 1968; Bruce 1989). CJD, scrapie, TME, and CWD show strain diversity, while BSE appears to
686 be a single, stable strain (Bruce 1994; Bruce 1997). vCJD (a disease in humans thought to result
687 from exposure to the BSE agent) does not demonstrate morphologic strains (Will 1996; Bruce
688 1997; Hill 1997; Scott 1999).

689

690 Recipient characteristics also affect the efficiency with which TSEs are transmitted
691 across species. Some species, such as rabbits or chickens, do not develop disease when
692 challenged with specific TSEs, while other species do. It has been postulated that the similarities
693 between the PrP structure between the donor and the recipient explain the differences in
694 transmission efficiency (Priola 1994; Raymond 2000).

695

696 Because the presence of a TSE agent is often assessed by inoculating a test species (*e.g.*,
697 mice) with the suspect material, the species barrier reduces the sensitivity of these bioassays.
698 Cattle-to-cattle transmission of BSE by the intracerebral route is estimated to be at least 1,000
699 times more efficient than cattle-to-mouse transmission by the same route (Section II.7 in
700 (European Union Scientific Steering Committee 2000a)). It is often assumed that the species
701 barrier decreases transmission efficiency by a factor of between 1 (no decrease) and 1,000 (Det
702 Norske Veritas 1997). The assumption that the species barrier is 1 (*i.e.*, that there is effectively
703 no species barrier) is considered to be a worst-case scenario. In an opinion on the species barrier
704 for transmission of BSE from cattle to humans, the EU Scientific Steering Committee (1999a)
705 suggested that plausible values for the species barrier range from 1 to 100,000. For risk
706 assessments, this range was later updated to include 1 as a worst case and a values from 10 to
707 10,000 as more likely (p. 35 in (European Union Scientific Steering Committee 2000a)).
708 However, the committee concluded that it is not at this time possible to quantify the species
709 barrier for transmission of BSE from cattle to humans (p. 34 in (European Union Scientific
710 Steering Committee 2000a)).

711

712 **2.1.3 Susceptibility**

713 "Susceptibility" refers to the likelihood of becoming infected following a specific
714 exposure to the infective agent. Susceptibility to TSEs appears to depend on specific interactions
715 between the agent, the host, and the environment (*e.g.*, animal age, PrP primary structure of the
716 host, PrP characteristics of the recipient animal, route of exposure, and dose of agent).

717

718 Mutations and polymorphisms of the PrP gene are associated with many TSEs in humans,
719 sheep, mice, and possibly elk. Humans and sheep are the two species for which spongiform
720 encephalopathies apparently occur naturally and in which there are recognized genetic
721 components that predispose individuals to disease. In the case of scrapie, there is evidence that
722 the disease does not develop spontaneously, but instead requires exposure to an infective agent
723 (Hunter 1996; Hunter 1998b). In the case of human disease, studies conducted using transgenic
724 mice that over express mutant PrP [P101L (corresponding to PrP P102L in humans)] have shown
725 that Gerstmann-Straüssler Skeinker might be a genetically induced illness (Hsiao 1991; Hsiao
726 1994). However, recent research using transgenic mice that are normal expressers of mutant PrP
727 failed to demonstrate development of the spontaneous TSE (Manson 1999), suggesting that the
728 mutation may increase susceptibility to infection (Manson 1999; Weissmann 1999), rather than
729 cause the disease on its own. In contrast, in cattle, susceptibility to BSE has not yet been shown
730 to be associated with polymorphism in the PrP gene (Hunter 1994).

731

732 An important physiologic factor that is likely to affect susceptibility to infection is the
733 age of the animal. For example, young cattle are estimated to be ten times more susceptible than
734 adults, with data well described by a model that assumes susceptibility declines exponentially
735 with an annual rate constant of 0.85 after the age of four months, and susceptibility ultimately
736 declining to 10% of its peak value (de Koeijer 1999). Wilesmith *et al.* (1988) described an
737 epidemiologic study of the UK BSE epidemic. Based on a model of that event, Anderson *et al.*
738 (1996) back-calculated an alternative susceptibility estimate suggesting that susceptibility peaks
739 at 1.31 years and decreases in the following years. Other investigators estimated that
740 susceptibility in cattle peaks at between 0.5 to 1.5 years of age (Woolhouse 1997). Age-related
741 susceptibility is hypothesized to be associated with permeability of the intestine to large proteins
742 and with the development of the Peyer's Patches (PP). The PP seem to play a role in the
743 pathogenesis of the prion diseases and to influence the susceptibility of the animal to infection.
744 For example, in sheep, the ileal PP are shown to be more active and to be largest when the animal
745 is around 2-3 months old and to disappear when the animal reaches an age of one and one-half
746 years (Griebel 1996). The appearance of the PP in sheep appears to coincide with the period of
747 greatest susceptibility of sheep to scrapie (Hadlow 1982; Andreoletti 2000).

748

749 Age-related susceptibility may be an important factor in understanding BSE transmission
750 because potential exposure to BSE-contaminated feed (see Section 2.2 and Section 3.1.1.2 below)

751 can also change with age. The ages at which animals are exposed depends on when they receive
752 feed with protein supplements, something that may vary from country to country. For instance,
753 Meat and Bone Meal (MBM) was used in the formulation of "least cost" calf starter rations in the
754 UK during the period of 1970-1988 (Horn 2001), leading to BSE exposure when animals are
755 most susceptible to disease.

756

757 The remainder of this discussion addresses susceptibility issues specific to sheep,
758 humans, bovines, and cervids in turn.

759

760 *Sheep*

761

762 In sheep, polymorphisms identified at codon 136, 174 and 171 of the PrP gene play the
763 largest role in variations in the development of natural scrapie. The clinical and pathological
764 variations of the disease are a direct result of host-agent interaction. Holding both dose and route
765 of transmission fixed, the transmission of scrapie depends on the homology of the donor's PrP
766 and the recipient's PrP. Some aspects of the pathogenesis can differ depending on the interaction
767 of agent strain, host genotype, route of infection, and dose of the agent.

768

769 Naturally infected sheep of a number of breeds in the U.S., UK, Europe, and Japan carry
770 valine at codon 136 (VV₁₃₆ or VA₁₃₆) or glutamine at codon 171 (QQ₁₇₁) (Hunter 1993; Laplanche
771 1993; Hunter 1994; Westaway 1994; Belt 1995; Ikeda 1995) of the PrP gene. There has only
772 been one report of scrapie-affected Suffolk sheep with arginine homozygosity at codon
773 171 (RR₁₇₁) and four reports of scrapie-affected Suffolk sheep with glutamine/arginine
774 heterozygosity at codon 171 (QR₁₇₁) (Ikeda 1995; Hunter 1997c). Scrapie strains can be
775 distinguished by biological parameters such as the incubation period, lesion profile, and amyloid
776 plaque production (Dickinson 1971; Bruce 1982; Dickinson 1988; Bruce 1991; Bruce 1997).

777

778 There has been some debate as to whether naturally occurring scrapie is a purely
779 genetically-induced disease (Ridley 1996) or if PrP genotype merely influences susceptibility
780 following exposure to an infectious agent. The current consensus rules out the hypothesis that
781 scrapie is a purely genetic disease (Hunter 1998a; Hunter 1998b) and suggests that susceptibility
782 and exposure are both necessary for the development of the disease.

783

784 Sheep and goats have been shown to be susceptible to the development of BSE following
785 experimental exposure (i.c. and oral) (Foster 1993; Bruce 1994; Foster 1996). Different PrP
786 genotypes have different incubation periods (Foster 2001) following BSE exposure. Currently,
787 there is no evidence that sheep and goats can develop the disease after exposure to feed
788 supplemented with contaminated animal protein.

789

790 *Humans*

791

792 In humans, polymorphisms in the PrP gene influence susceptibility to sporadic, inherited,
793 or infectious forms of prion diseases. There are two common forms of PrP in humans with either
794 methionine (M) or valine (V) at residue 129. The population is comprised of homozygous M,
795 heterozygous M-V, and homozygous V. In Caucasians, 51% of the population are heterozygous,
796 while 38% are methionine homozygous; the least common genotype is valine homozygous
797 (11%). Variability of spontaneous CJD seems to be associated with physicochemical properties
798 of PrP^{sc} in conjunction with the *PRNP* (human prion protein gene) codon 129 genotype (Parchi
799 1999). In Kuru patients, homozygosity at residue 129 (particularly for methionine) was
800 associated with an earlier age at onset and a shorter duration of illness than was heterozygosity at
801 residue 129, a finding that probably reflects different disease incubation periods (Cervenakova
802 1998).

803

804 Homozygosity at residue 129 appears to increase susceptibility to TSE disease in
805 humans. Cases of sporadic CJD are usually homozygous at residue 129 (Palmer 1991).
806 Individuals with CJD caused by exposure to contaminated human pituitary hormone have an
807 elevated prevalence of homozygosity at residue 129 for valine (Collinge 1991). In familial TSEs,
808 polymorphism at codon 129 appears to influence the age of onset and the duration of the disease
809 (Dlouhy 1992). To date, all vCJD patients have been methionine homozygous (M-M) at residue
810 129 (Ironsides 2000; Will 2000).

811

812 *Bovines*

813

814 Investigators have identified polymorphisms in the PrP gene in British cattle, Belgian
815 cattle, and US cattle (for a review refer to (European Union Scientific Steering Committee
816 2000a)). There are two major polymorphisms in the region of the PrP gene: 1) the HindII

817 restriction site, and 2) differences in the number of copies (five or six) of an octapeptide repeat
818 sequence (Goldmann 1991; Hunter 1994).

819

820 Hunter *et al.* (1992) showed that there were no differences among breeds in the age of
821 onset of BSE. Nor did the number of PrP octapeptide copies influence age of onset. The absence
822 of an association between PrP polymorphisms and BSE onset age may indicate that BSE
823 incidence is associated with an “undiscovered” polymorphism of the PrP gene. It could also
824 mean that there are other mutations that influence gene expression and potentially disease onset.
825 Alternatively, there may be only one predominant form of cattle PrP, and if this predominant
826 form were the allele that conferred susceptibility, most cattle would be genetically susceptible. In
827 this case, the dose and route of exposure (assuming there is only one strain of BSE) determine
828 whether disease results.

829

830 Findings from the pathogenesis and the attack rate experiments (Wells 1998; Wells
831 1999), in which animals were exposed to high levels of infectivity (1 to 100 times greater than
832 most cattle would have received naturally), indicate that most of the cattle challenged either
833 orally or parenterally succumbed to disease. These results suggest that differences in
834 susceptibility between animals may not exist, or may not be important. Alternatively, the
835 exposures may have been so high that they overwhelmed any differences in susceptibility.
836 Overall, it appears that if animals are exposed to high doses of the BSE agent early in life, they
837 will be very likely to develop disease.

838

839 Cattle have been shown to be partially susceptible to naturally induced scrapie but only
840 following intracerebral injection of infectious material (Gibbs 1990; Cutlip 1994; Clark 1995;
841 Cutlip 1997; Cutlip 2001). Studies done in the U.S. showed that cattle orally exposed to North
842 American scrapie remain normal for eight years following exposure (Cutlip 2001). Research on
843 cattle orally exposed to UK scrapie is ongoing (Detwiler 2000). Currently, there are no available
844 data indicating how genetics might influence bovine susceptibility to scrapie.

845

846 *Cervids*

847

848 In a study of Rocky Mountain Elk, O'Rourke *et al.* (1999) found that animals with CWD
849 had an elevated prevalence of homzygosity for methionine at codon 132 of the PrP gene. This
850 finding applied to both farmed and free-range animals.

851

852 **2.2 The Origin of the BSE Epidemic in the UK**

853 In 1986, a bovine spongiform encephalopathy was first confirmed in the United Kingdom
854 as the result of routine animal disease surveillance. This section focuses on theories advanced to
855 explain the origins of the subsequent epidemic. Since the beginning of the epidemic, over
856 178,400 cases have been confirmed on 35,275 farms. In addition, cases have been observed in
857 Northern Ireland, the Republic of Ireland, and in other European countries (OIE 2000).
858 Mathematical modeling suggests that the epidemic probably started in the UK between 1981 and
859 1982 (Wilesmith 1991; Wilesmith 1992b; Wilesmith 1994; Donnelly 1997b; Ferguson 1997b;
860 Ferguson 1999). The epidemic peaked at the end of 1992-1993 when the incidence reached
861 approximately 3,500 confirmed cases per month. Although the origin of the BSE epidemic
862 remains controversial, there is little doubt that it was maintained by the recycling of bovine
863 materials in the bovine feed chain (Wilesmith 1991; Wilesmith 1992b; Kimberlin 1994;
864 Wilesmith 1994; Nathanson 1997).

865

866 Although the effectiveness of the feed ban and other measures at reducing the incidence
867 of BSE in the UK sheds light on the progress and amplification of this epidemic (Section 2.4.2),
868 its precise origin remains uncertain (Wilesmith 1991; Wilesmith 1992a; Wilesmith 1993;
869 Hoinville 1994; Brown 1998a). The most prominent theory hypothesizes that BSE occurred
870 when the scrapie agent, present in rendered proteins used in feed, overcame the species barrier to
871 infect cattle (Section 2.2.1). Several changes in rendering and feeding practices may have
872 enabled the infectious agent to survive during rendering process and enter the cattle feed chain
873 (Taylor 1989; Horn 2001). An alternative theory postulates a spontaneous case of BSE as the
874 origin (Section 2.2.2). Section 2.3.1 discusses spontaneous disease in further detail. Additional
875 theories focus on different infectious organisms or toxic agents that could cause a spongiform
876 encephalopathy or on dietary imbalances known to produce spongiform encephalopathies under
877 some conditions (Section 2.2.3).

878

879 **2.2.1 Scrapie in Sheep**

880 Evaluating the hypothesis that scrapie is responsible for the BSE epidemic in the UK is
881 complicated because even transmission of this disease among sheep is not well understood.
882 Horizontal transmission may involve the shedding of the agent into the environment (Hoinville
883 1996; Stringer 1998; Woolhouse 1998). Maternal transmission from ewe to lamb in utero or

884 immediately during the post-natal period is believed to occur, although there has been some
885 debate in the past (Ridley 1996). Maternal transmission of scrapie may explain why the disease
886 usually becomes endemic in a flock once it is introduced. Exposure through contaminated
887 vaccines (Gordon 1939; Gordon 1946; Gordon 1959; Agrimi 1999; Caramelli 2001) has been
888 documented as a source of infection. Transmission of scrapie *via* vectors is disputed
889 (Fitzsimmons 1968; Hourrigan 1979).

890

891 The possibility that scrapie is responsible for the BSE epidemic in the UK is made more
892 plausible because the size of the sheep population in the UK increased significantly from 1980
893 onwards. This growth may have led to an increase in the prevalence of scrapie, a disease with
894 an annual incidence now estimated to be between 5,000 and 10,000 per year in the UK (Hoinville
895 1999). Moreover, it has been postulated that more scrapie-infected sheep than usual were
896 introduced into the cattle feed supply during this period (Walker 1991). In addition, changes in
897 the rendering technology in the 1980s may have made this process less effective at deactivating
898 the scrapie agent. During that time, meat and bone meal (MBM) was on the list of ingredients for
899 “least cost” dairy calf starter rations and was regularly used as a source of alternative protein. If
900 the species barrier can indeed be overcome by exposure to a sufficiently large amount of
901 infectivity, and if young animals are especially susceptible to infection, these changes may have
902 been sufficient to initiate the development of BSE in cattle. Once in cattle, according to this
903 theory, the agent adapted, thus eliminating the species barrier, and quickly spread to other cattle
904 through feed containing rendered ruminant material.

905

906 One finding supporting this theory is the observation that BSE apparently originated at
907 several locations at nearly the same time (Kimberlin 1994; Wilesmith 1994; Nathanson 1997).
908 Such a pattern suggests some sort of population-wide insult, such as a large supply of
909 ineffectively treated feed containing scrapie. This theory also is supported by the finding that
910 cattle are susceptible to infection by scrapie introduced by i.c. experimental inoculation. On the
911 other hand, investigators have been unable to infect cattle with the North American scrapie agent
912 when it has been orally introduced (Cutlip 1994; Cutlip 1997; Cutlip 2001); research is ongoing
913 using the UK scrapie agent (Detwiler 2000). In addition, if scrapie did cause the development of
914 BSE in cattle, it is not clear why it happened suddenly in 1986 at several locations given that
915 scrapie has been endemic in European sheep for over 250 years and ovine and bovine wastes have
916 been used in cattle feed for several decades. In response to that question, attention has focused on
917 the use of MBM in dairy calf starter rations, feed given to very young animals (Horn 2001). This

918 practice, which is not likely to have taken place elsewhere (except in Australia, which is a
919 scrapie-free country) would have exposed animals to infectivity when they are most susceptible.
920 Finally, if scrapie caused BSE to originate at several locations at nearly the same time, it is
921 surprising that there is only a single strain of BSE even though sheep in the UK are known to
922 carry several “strains” of scrapie.

923

924 One variation on the scrapie hypothesis suggests the existence of a strain of scrapie that
925 was more thermostable and particularly infectious to cattle. This theory suggests that this strain
926 may have entered the cattle feed chain as a component of MBM. The specific strain may have
927 been a mutation of the scrapie agent. It is possible that either: 1) a single scrapie strain with
928 characteristics unlike BSE was transmitted to cattle and that these characteristics changed as the
929 agent was repeatedly recycled through cattle; or 2) a BSE strain pre-existed in sheep, and was
930 unchanged when passed to cattle. These hypotheses are both plausible. However, if the origin of
931 BSE was a single “strain” of scrapie, the BSE epidemic should have had a more geographically
932 compact origin than the diffuse pattern actually observed, unless the single “strain” was widely
933 distributed. BSE epidemiology shows a geographically widespread occurrence with simultaneous
934 onset at multiple distant locations, rather than an origin focused at a single point. Finally, this
935 alternative theory does not address the lack of a demonstration to date of *any* strain of scrapie that
936 can infect cattle following oral administration (Cutlip 2001).

937

938 **2.2.2 Infrequent Sporadic BSE**

939 It is possible that BSE is a naturally occurring and long-established disease of cattle, but
940 one that occurs extremely rarely (like sporadic CJD in humans). Passing infectious material from
941 such an animal through a rendering process with greatly reduced capacity for destroying the agent
942 could have led to contamination of the cattle feed chain. However, many countries had rendering
943 systems similar to that of UK, so the absence of BSE in other countries, if it is indeed sporadic,
944 seems unlikely. That is, we would expect to see native cases in other countries as well (*i.e.*, cases
945 not traceable to UK). To date, none have been found (for a review see (Chesebro 1999).

946

947 On the other hand, the cattle in the UK tend to be relatively old, with many dairy animals
948 in particular of relatively advanced age. If sporadic BSE resembles sporadic CJD in humans, its
949 incidence will be much greater in older animals. As a result, the UK herd may have been
950 predisposed to having an animal with sporadic disease approaching the highly infectious

951 symptomatic stage of disease. The sporadic case theory postulates that a series of unfortunate
952 events would have had to coincide: 1) the rare sporadic case would have had to have been
953 rendered; 2) the rendering would have had to leave enough of the infectivity intact to produce a
954 sufficient number of "second generation cases"; 3) the rendered material would have had to have
955 been used to produce feed for cattle; and 4) the repetition of this cycle. The apparent uniqueness
956 of the UK as the origin of this disease may simply reflect better fortune in other countries.

957

958 **2.2.3 Toxic Agents and Other Hypotheses**

959 This section describes several alternative agents and conditions that have been suggested
960 as possible causes of the BSE epidemic in the UK.

961

962 **2.2.3.1 Organophosphate (OP) Pesticides**

963 Organophosphate (OP) pesticide toxicity in cattle may resemble BSE, and like BSE, the
964 clinical signs for OP toxicity exhibits seasonality. It has been suggested that there was a link
965 between the use of some OP pesticides, especially Phosmet, and the development of BSE (Purdey
966 1996). Adherents to this theory claim that the distribution and dynamics of the use of the
967 pesticide are consistent with the epidemiology of the BSE epidemic in UK. However, the timing
968 of the BSE epidemic's origin does not coincide with the extensive use of OPs in the early 1960s
969 for warble fly control because most of the BSE cases were born after 1982. This hypothesis
970 rejects the evidence that contaminated MBM plays a role in the transmission of the disease.

971

972 Purdey, the author of this theory, proposes that exposure of bovine embryos to high doses
973 of Phosmet triggered the UK BSE epidemic (Purdey 1996). The mechanism underlying this
974 theory is the phosphorylation of PrP in fetuses of cows treated with Phosmet. The Spongiform
975 Encephalopathy Advisory Committee (SEAC) concluded, however, that OP pesticides did not
976 accumulate in cattle, which would be necessary for the transmission of the disease via
977 contaminated feed. The committee agreed that the epidemiological evidence is more consistent
978 with the hypothesis that the BSE epidemic was due to the widespread use of BSE-contaminated
979 feedstuffs (Spongiform Encephalopathy Advisory Committee 1997). The EU Scientific Steering
980 Committee (SSC) evaluated this hypothesis and determined that intoxication with OP compounds
981 was consistent with some of the characteristics of the BSE epidemic but could not be considered
982 to be the cause (European Union Scientific Steering Committee 1998a). In particular, this theory

983 fails to account for the presence of BSE cases in areas of UK that did not use OPs (Horn 2001),
984 the absence of cases in areas of UK that did use OPs (Horn 2001), and the absence of cases in
985 countries that use OPs more extensively than the UK. In addition, OP exposure has not been
986 shown to be transmissible.

987

988 **2.2.3.2 Copper Deficiency**

989 The incidence of BSE in the UK was highest in the southern and eastern counties of
990 England (Wilesmith 1991; Wilesmith 1992b). Several counties in this region are known to have
991 widespread copper deficiencies in soils and crops (Thornton 1979). These deficiencies could
992 cause copper deficiency in ruminants. The resulting condition is known to have some specific
993 signs and pathological changes similar to those of BSE.

994

995 One theory for the origin of the BSE epidemic hypothesizes that the high levels of protein
996 in feed used in the 1970s and 1980s competed with copper for absorption by ruminants
997 (Rehbinder 1994). This theory is consistent with some aspects of the disease, but the morphology
998 and distribution of vacuolar or spongiform-like changes observed in animals suffering from
999 copper deficiency differ from the spongiform changes that are typical of a TSE (Annex 6 in
1000 (European Union Scientific Steering Committee 2000b)). This theory also fails to account for the
1001 disease's transmissibility. Furthermore, if this hypothesis were valid, beef cows (that obtain most
1002 of their nutrients through pasture) should have a higher incidence of BSE than dairy cattle, and
1003 the reverse is observed (Horn 2001).

1004

1005 **2.2.3.3 Heavy Metal Exposure**

1006 The role of heavy metals in certain CNS diseases (Warren 1974) has led some researchers
1007 to suggest they may have a role in the development of BSE. It has been shown that copper ions
1008 can convert PrP to the infective disease form (McKenzie 1998). Investigators have suggested that
1009 contamination of MBM with heavy metals may have converted the normal PrP to the infective
1010 form. However, this theory is inconsistent with the characteristics of the epidemic in UK because
1011 heavy metal exposure is likely in areas where BSE has never been observed. Moreover, a
1012 potential source of heavy metal contamination of feed has never been identified, nor has
1013 transmissibility been demonstrated.

1014

1015 2.2.3.4 Autoimmune Disease

1016 Investigators have proposed that BSE could be an autoimmune disease caused by
1017 exposure of cattle to bacteria containing proteins that induce immunologic cross-reactivity with
1018 central nervous system tissue (Ebringer 1997; Tiwana 1999). According to this theory, the BSE
1019 epidemic resulted from the production of feed rich in the specific bacteria with proteins that
1020 mimic brain tissue. Because of exposure to these bacteria, bovine anti-bacterial antibodies may
1021 have reacted with myelin proteins in the brain that were sufficiently similar to bacterial antigens.
1022 The damage caused by such an auto-immune disease would be chronic and would be consistent
1023 with some of the characteristics of BSE (European Union Scientific Steering Committee 2000b).
1024 Autoimmune brain disease can be experimentally transmitted to animals but only by injecting
1025 large amounts of brain protein and adjuvants. In contrast, TSE can be transmitted by injecting
1026 only a few nanograms of brain without adjuvant (Horn 2001). In addition, the neuropathology of
1027 autoimmune brain disease differs from that observed in TSE.

1028

1029 SSC has concluded that this theory is not consistent with the BSE epidemic for several
1030 reasons. First, the morphology and distribution of vacuolar or spongiform-like changes due to
1031 BSE are not the same as those caused by an auto-immune reaction. Second, lymphocytic
1032 infiltrates that are typical of and are a pathogenetically important component of auto-immune
1033 disease are atypical of TSE. Third, high infectious titers cannot be explained by the autoimmune
1034 hypothesis (European Union Scientific Steering Committee 2000b). Fourth, as pointed out by the
1035 BSE Inquiry (Lord Phillips 2000), mouse-adapted BSE can be transmitted i.c. to mice lacking a
1036 functional immune system. Fifth, common bacteria do not have the resistance to chemical and
1037 physical inactivation shown by the agents of transmissible spongiform encephalopathies,
1038 including bovine spongiform encephalopathy. Finally, this theory fails to explain why many
1039 thousands of animals suddenly became affected and why the BSE epidemic occurred
1040 predominantly in the UK (Horn 2001).

1041

1042 2.2.3.5 Use of Pituitary Hormones

1043 Posterior pituitary extracts obtained from oxen or other mammals were used as a source
1044 of oxytocin for veterinary purposes through the period 1950-1989. Use of anterior pituitary
1045 extracts as a source of follicle stimulating hormone or bovine growth hormone occurred but was
1046 not widespread (Horn 2001). Early epidemiologic investigations of the BSE outbreak dismissed
1047 hormone extracts as a cause of the disease's spread (Wilesmith 1988). Recall that growth

1048 hormone, prepared from cadaver pituitary glands, has caused transmission of CJD in humans, and
1049 this theory suggests that a similar phenomenon may have occurred in cattle (Airtime 2001). This
1050 hypothesis suggests that pituitary hormones contaminated by BSE caused the epidemic in the UK
1051 but not in other countries. The source of the original infectivity (in humans it was one or more
1052 pituitaries from CJD cases) is not explained by this theory.

1053

1054 **2.2.3.6 Wild African Antelope**

1055 A group of scientists from New Zealand postulated that BSE originated from wild
1056 African antelope, and that it spread into British cattle when an infected animal from a wildlife
1057 park was rendered into MBM that was fed to about 1,000 dairy cows in the southwest of England
1058 between 1975 and 1977 (ProMED-mail 2001, April 18). They hypothesized that the disease
1059 probably spread through British cattle for about a decade before it was fully recognized. Kelly et
1060 al. (1980) suggested that the death of six white tigers in a British zoo was due to TSE but the
1061 histopathology was not consistent with BSE (Horn 2001). This theory is not consistent with the
1062 absence of evidence that carnivores in zoos in the UK were dying from TSE-like symptoms
1063 before 1986. In addition, there is no evidence that any TSE exists in the wildlife of Africa (Horn
1064 2001).

1065

1066 **2.3 Sources of BSE Infectivity**

1067 This section describes potential sources and pathways by which BSE infectivity could be
1068 introduced into the U.S., including the development of a spontaneous BSE case (Section 2.3.1),
1069 the import of an infected animal into the U.S. (Section 2.3.2), scrapie (Section 2.3.3), oral
1070 ingestion of tissue or material containing chronic wasting disease infectivity (Section 2.3.4),
1071 horizontal or lateral transmission of chronic wasting disease (Section 2.3.5), transmissible mink
1072 encephalopathy (Section 2.3.6), TSEs in pigs (Section 2.3.7), TSEs in chickens (Section 2.3.8),
1073 and contamination from recycled products, including plate waste, gelatin, milk, blood and blood
1074 products, and tallow (Section 2.3.9).

1075

1076 **2.3.1 Spontaneous BSE**

1077 A potential way in which BSE could be introduced into the United States is the
1078 development of a spontaneous case of a BSE in a native animal. A “spontaneous case” is one that
1079 occurs in an animal with no known risk factors for development of BSE. The presumed

Section 2

1080 mechanism by which a BSE could occur spontaneously is by the mutation of the PrP gene to a
1081 form that codes for PrP^{sc}, and subsequent recruitment of PrP^c until disease is manifest (Prusiner
1082 1989); (for a review see: (Chesebro 1999). There is no direct evidence of this mechanism,
1083 although some argue that all mammals might have a low spontaneous rate of TSE (Hueston
1084 1997). In addition, a transgenic animal over-expressing the PrP gene has apparently replicated
1085 the human TSE GSS (Hsiao 1991). Recent results, in which mice expressing the same point
1086 mutation but at normal levels failed to develop disease (Manson 1999), suggest the mutations
1087 may increase susceptibility rather than directly cause the disease. Although at this time there is
1088 no scientific evidence suggesting that spontaneous BSE exists, the BSE Inquiry suggested that
1089 TSEs could possibly develop sporadically in other species, as they do in humans (BSE Inquiry
1090 2000a). In contrast, the Review of the origin of BSE (Horn 2001) concluded that although the
1091 spontaneous case hypothesis cannot be excluded, there is no evidence supporting the presence of
1092 sporadic form prion disease in cattle or sheep.

1093

1094 It is not possible to determine for any particular TSE whether the original cause was a
1095 mutation or transmission of disease from another species or from the same species. For example,
1096 transmissible mink encephalopathy (TME) has no known origin. There are a number of theories,
1097 most of which focus on transmission from another species (Marsh 1991). In the case of BSE,
1098 there is little evidence from the epidemiology to suggest that cases arise without some exposure
1099 to infectivity (Wilesmith 1991; Kimberlin 1994; Horn 2001). On the other hand, there are a small
1100 number of cases for which there are no known risk factors in the UK (MAFF (Ministry of
1101 Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) 2000) and
1102 in Denmark (Tegtmeier 2001).

1103

1104 The existence of a spontaneous form of TSEs in animals is controversial. In humans,
1105 cases of CJD in persons with no known risk factors or exposure to the disease occur at an annual
1106 incidence of approximately one per million. The incidence appears to be relatively constant
1107 around the world, regardless of diet, environment, or other factors that may hypothetically
1108 influence disease rates. Cases in individuals with no known risk factors are often referred to as
1109 "sporadic CJD." The etiology of sporadic CJD is unknown. Sporadic CJD appears almost
1110 exclusively in humans more than 50 years old. Cases appear to occur without a predictable
1111 epidemiological pattern (Will 1986; Brown 1994b). Sporadic CJD accounts for 85% of all cases
1112 and these cases are characterized by a clinical course that is relatively rapid, although rare
1113 variants have shown an extensive duration of clinical illness (Brown 1984). It is sometimes

1114 asserted that the rate of sporadic CJD in humans is likely to be representative of the rate of
1115 spontaneous BSE in cattle (Biopharm 1997), although the rate in cattle has never been directly
1116 measured and may in fact be zero.

1117

1118 **2.3.2 Import of BSE Infectivity into the United States**

1119 This section describes the potential for the import of BSE infectivity into the U.S., in the
1120 form of either infected live cattle (Section 2.3.2.1) or contaminated feed material (Section
1121 2.3.2.2).

1122

1123 **2.3.2.1 Imported Live Cattle from the UK**

1124 The U.S. imported animals from the UK during that country's BSE epidemic. Between
1125 January 1, 1981, and July 1989, the United States imported 334 cattle from the UK. Ninety-six
1126 percent of these animals were beef breeding stock, while the remaining four percent were dairy
1127 cattle. In 1989, the U.S. prohibited the import of ruminants from countries affected by BSE.

1128

1129 Of the 334 UK imports, 161 were disposed of in a manner that eliminates the possibility
1130 that they could have contaminated either human food or animal feed. The remaining 173 cattle
1131 were imported before the peak of the epidemic, and none came from a birth cohort in which a
1132 BSE case is known to have developed (Detwiler 2001). Of these 173, 164 (94.8%) were beef
1133 breeding animals and nine (5.2 %) were dairy animals. It is possible that remains from some of
1134 the 173 cattle imported from the UK between 1980 and 1989 could have ended up in either
1135 animal feed, human food, or both. Section 3.4.3 describes our risk assessment of this scenario.

1136

1137 **2.3.2.2 Imported Cattle from Continental Europe**

1138 Between 1983 and 1987 397 breeding cattle were imported from Switzerland, France,
1139 Italy, and Belgium. These animals were beef breeds except for ten dairy animals imported from
1140 France in 1984. From 1996 to 1997, there were also 46 animals imported from Belgium,
1141 Germany, Austria and Italy. Because the vast majority of the imports from continental Europe
1142 occurred before 1988, they pose only a limited risk to the U.S. All animals imported after 1996
1143 have been traced and their movements controlled. There is therefore virtually no risk that these
1144 imports introduced BSE into the U.S. cattle population. Finally, two head of cattle imported from
1145 Belgium in 1996 are also under quarantine.

1146

1147

2.3.2.3 Imported Cattle from Non-European Countries

1148

1149

1150

1151

1152

1153

1154

1155

2.3.2.4 Imported MBM and Feed

1156

1157

1158

1159

1160

1161

1162

1163

1164

1165

1166

1167

1168

1169

1170

1171

1172

1173

1174

1175

1176

1177

1178

It is estimated that since 1986, the U.S. has imported from Canada and Mexico between 750,000 and 2.5 million animals annually. The vast majority of the cattle (at least 80%) are animals for feeding or slaughter. The cattle imported from Canada for immediate slaughter are sent to slaughterhouses in sealed trucks. All identification is collected at the time of slaughter and they are noted as animals of Canadian origin. These imports are extremely unlikely to pose a risk of introducing BSE into the U.S.

There are no reliable data documenting the type and composition of feed imported into the U.S. between 1980 and 1990. Current APHIS regulations prohibit the import of ruminant meat and edible products produced from animals in regions where BSE has been documented.

USDA reports that no MBM was imported from the UK between 1980 and 1990. Since 1989, MBM has been imported from New Zealand, Canada, Chile, Peru, and Australia. Most MBM came from Canada (an average of 25,000 metric tons per year). Chile exported to the U.S. only 3,000 metric tons of MBM in 1989. Peru exported 15,000 metric tons of MBM to the U.S. in 1989 and 4,000 metric tons in 1990. Panama exported 7,000 metric tons of MBM in 1989 and 4,000 tons in 1990. It is important to note that: 1) the U.S. produces approximately 60% of the rendered materials generated globally (Rudbeck 1999); 2) the U.S. is mainly an exporter of MBM; and 3) shipping MBM to the U.S. from overseas is unlikely to be economically competitive (Franco 2001).

The geographical assessment of BSE in the U.S. (European Union Scientific Steering Committee 2000d) reported the export of mammalian meal and flour from the UK in 1981 (12 tons), 1984 (10 tons), 1985 (2 tons), 1989 (20 tons), and 1997 (37 tons). The U.S. does not have corresponding import statistics for 1989 (USDA-APHIS 2000). It is likely that the materials imported in 1997 included non-mammalian protein because the UK Overseas Trade statistics did not specifically report separate values for MBM, but instead subsumes this material in the category, "*flours and meals of meat and offals, unfit for human consumption, greaves*". In addition, since the adoption of the Commission Decision 93/239/EC on March 27, 1996, it has been illegal to export from the UK meat meal, bone meal, and MBM derived from mammals.

1179 MBM imported prior to the peak of the epidemic in the UK is not thought to pose a substantial
1180 BSE risk. Most importantly, MBM is used for pet food and other products and poses little
1181 exposure risk to cattle. Finally, although it is possible that MBM from the UK entered the U.S.
1182 *via* a third country, there is no evidence that has occurred. In summary, past MBM imports pose
1183 little risk of exposing U.S. cattle to BSE.

1184

1185 **2.3.3 Domestic Scrapie**

1186 The first case of scrapie diagnosed in the U.S. occurred in 1947. Various control and
1187 eradication programs have existed since 1952 when the disease became nationally reportable. At
1188 that time, when the disease was confirmed in a flock, the flock was quarantined and then
1189 depopulated. In 1957, the regulations were amended to include location and subsequent
1190 depopulation of the of source flocks. Different surveillance approaches have been instituted since
1191 that time (*e.g.*, the bloodline surveillance program and reporting incentives). The Voluntary
1192 Scrapie Flock Certification Program, approved in 1997 was designed to monitor flocks and
1193 certify the status of the animals enrolled in the program (U.S. Department of Agriculture 2000).
1194 This program is still in effect.

1195

1196 The precise prevalence of scrapie in sheep in the U.S. is unknown. It is likely that
1197 changes in the national scrapie control and eradication program affected the reporting of
1198 potentially infected sheep. Statistics from the period between 1947 and 1992 indicate that during
1199 this period, there were a total of 1,117 affected sheep from 657 flocks located in 39 states
1200 (Wineland 1998). The number of scrapie-positive flocks increased slightly between 1965 and
1201 1992, probably reflecting changes in reporting protocols and changes in incentives offered to
1202 farmers to report affected animals. One hundred sixty-eight rams and 949 ewes were also
1203 reported to be scrapie-positive during the study period. Annual mortality due to scrapie in a flock
1204 is usually low (three to five percent), although higher mortality rates of up to 50% have been
1205 reported (Detwiler 1992). In Great Britain, the prevalence of detectable scrapie infection in the
1206 slaughter population was estimated to be 0.11% in 1997/1998. This detectable rate probably
1207 corresponds to a true infection prevalence in the same population of up to 11% (Webb 2001).
1208 Table 2-1 details the number of sheep condemned with scrapie in the U.S.

1209

1210
1211
1212
1213

Table 2-1
Sheep Condemned With Scrapie in the United States:
Fiscal Year 1998

Animal Category	Number Slaughtered	Number Condemned	Percent Condemned
Mature Sheep	181,615	3,480	1.92
Lambs and Yearlings	3,272,844	3794	0.12
Goats	396,473	1505	0.38

1214

1215 The epidemiology of scrapie in the U.S. has reflected changes in the surveillance of the
1216 disease, reporting requirements, and in reporting incentives. The geographic concentration of
1217 scrapie-positive flocks in certain states has been attributed to the level of surveillance conducted
1218 within those states. No seasonal incidence pattern has been associated with scrapie.

1219

1220 The BSE epidemic in the UK influenced the processing of animal proteins in the United
1221 States. In 1989, the National Renderers Association (NRA) and the American Protein Producers
1222 Industry (APPI) recommended a voluntary ban on the processing of dead sheep. Consequently,
1223 the proportion of renderers processing inedible sheep offal also declined (Eastern Research Group
1224 1996). Later, the FDA prohibited the use of all ruminant proteins in ruminant feed (U.S. Food
1225 and Drug Administration 1997).

1226

1227 **2.3.4 Chronic Wasting Disease: Oral Exposure**

1228 Chronic-wasting disease (CWD) is a spongiform encephalopathy recognized for the first
1229 time in captive deer at a Colorado research facility in 1967 and later in Rocky Mountain elk at a
1230 Wyoming research facility in 1978 (Williams 1980). Additionally, CWD was confirmed in mule
1231 deer in 1977 (Williams 1980), and in free-ranging deer and elk in a five county region in
1232 Colorado and Southeastern Wyoming (Williams 1982). In high-risk areas, the prevalence of the
1233 disease is estimated to be between five and six percent, and in the surrounding areas, the
1234 prevalence is estimated to be around one percent (Miller 2000). Outside the U.S., CWD has been
1235 diagnosed on game ranches in Saskatchewan, Canada since 1996. In 2001, the Canadian Food
1236 Inspection Agency (CFIA) confirmed that a wild mule deer in Saskatchewan had tested positive
1237 for CWD (Venter 2001), representing the first case of CWD in the wild animal population in
1238 Canada (Canadian Food Inspection Agency Animal Products Animal Health and Production
1239 2001).

1240

1241 CWD is characterized by a progressive loss of body condition and by neurologic changes.
1242 It is believed that the infection is passed between animals *via* horizontal transmission. Most of
1243 the animals dying naturally from the disease are between the ages of two and seven years.
1244 Polymorphism in the PrP gene in elk has been associated with changes in the susceptibility to
1245 infection (O'Rourke 1999). Extensive nationwide surveillance started in 1997 in an effort to
1246 better understand the geographic location and magnitude of the problem (U.S. Department of
1247 Agriculture 2001a).

1248

1249 A small number of deer are commercially slaughtered for human consumption every year
1250 (U.S. Department of Agriculture 1998). These animals are usually younger than 1.6 years and are
1251 not likely to be recycled into ruminant feed (Floyd 2001). Hunters often process the cervids they
1252 kill themselves or use local butchers. In these cases, high-risk materials may be further processed
1253 at a prohibited rendering facility. Game deer are fed with protein supplements that contain small
1254 amounts of vegetable supplemental protein (Floyd 2001).

1255

1256 Although CWD has been transmitted to cattle *via* i.c. inoculation, transmission by natural
1257 routes to cattle is very unlikely to occur (Hamir 2001). For example, cattle orally inoculated with
1258 CWD infected brains have not shown any evidence of infection (Williams 2001). *In vitro*
1259 experiments investigating the conversion of bovine PrP^c by PrP^{CWD} suggest evidence of a
1260 molecular barrier limiting the susceptibility of cattle (Raymond 2000). Moreover, even if CWD
1261 could be transmitted to cattle, it is not clear it could cause BSE. For example, preliminary
1262 analysis of intracerebral inoculation of cattle with CWD revealed no typical TSE lesions in brain
1263 but did reveal the presence of PrP^{sc} by immunohistochemistry, Western Blot, and electron
1264 microscopy in three animals 22-27 months post-inoculation (Hamir 2001).

1265

1266 Even if CWD exposure can cause BSE, it is likely that the species barrier is substantial.
1267 *In vitro* assays have suggested that homology between an infectious and endogenous PrP
1268 molecule influences the rate and likelihood of conversion from PrP^c to PrP^{sc}, allowing the TSE
1269 disease to develop in the host (Priola 1994). *In vitro* studies have also shown differences between
1270 bovine PrP and PrP^{CWD} and these differences may represent a substantial species barrier. For
1271 example, Raymond et al. (Raymond 2000) reported that the cell-free conversion efficiency
1272 between bovine PrP^c and PrP^{CWD} is between five and twelve orders of magnitude weaker than
1273 inter-cervid transmission. This finding suggests that the species barrier may be between 10⁵ and
1274 10¹² (Raymond 2000).

1275

1276 Ascertaining the potential risk posed by oral exposure to CWD is further complicated by
1277 the following sources of uncertainty. First, there are no accurate statistics documenting the
1278 number or type of deer and elk killed by hunters. Second, the type of deer and elk that can be
1279 hunted in different geographic areas varies. Third, the disposition of deer and elk remains after
1280 slaughter is uncertain. Finally, the prevalence of the disease in all but the highest risk areas is
1281 unknown.

1282

1283 **2.3.5 Chronic Wasting Disease: Lateral Transmission**

1284 Direct contact between cattle and cervids in regions where CWD is prevalent may
1285 provide another pathway by which cattle may become infected. Epidemiologic modeling
1286 suggests that among cervids, environmental contact provides a pathway for the spread of CWD
1287 (Miller 2000). Moreover, the prevalence of the disease under experimental conditions appears to
1288 be extraordinarily high. For instance, when deer within the endemic research facilities have been
1289 introduced into CWD negative deer herds, the disease quickly reaches a prevalence of 50% to
1290 60% (U.S. Food and Drug Administration 2001a).

1291

1292 Nonetheless, there is no evidence that CWD can cause TSEs in cattle. As noted in
1293 Section 2.3.4, any such transmission would be limited by what appears to be a substantial species
1294 barrier. Moreover, cattle cohabiting with CWD infected deer and elk in a research facility in the
1295 endemic area have shown no evidence of infection (Williams 2001). Finally, targeted
1296 surveillance of cattle brains (by immunohistochemistry and histopathology) from endemic areas
1297 have failed to reveal the presence of CWD or any other TSEs (Gould 2000).

1298

1299 **2.3.6 Mink**

1300 Transmissible Mink Encephalopathy (TME) is a rare disease known to occur only in
1301 farm-raised mink. Epidemiological studies have suggested that TME is a foodborne disease with
1302 an incubation period of between seven months and a year (Hartsough 1965). The disease is
1303 characterized by a long incubation period, a clinical course of several weeks, and neurological
1304 changes. Mink experience increased aggressiveness, hyperexcitability, ataxia, and hyperaesthesia.
1305 Cases in Wisconsin and Minnesota were recognized on mink ranches as early as 1947. Outbreaks
1306 have been reported in Ohio, Canada, Finland, Germany, and Russia. Five outbreaks have been
1307 recorded in the U.S., affecting a total of 23 mink ranches (Hartsough 1965; Hadlow 1987; Marsh

1308 1991). Three of the outbreaks in Wisconsin were associated with the use of fallen or sick cattle in
1309 mink feed (Hartsough 1965; Marsh 1991). However, there is no consensus over the source of
1310 disease initiating these outbreaks. The rancher involved in the Stetsonville, Wisconsin outbreak
1311 claimed that his mink were fed only dead stock and that they were never fed sheep.

1312

1313 In theory, transmission of TME to a bovine could cause BSE. Inoculation of cattle with
1314 TME *via i.c.* administration resulted in spongiform encephalopathy a short time later (Marsh
1315 1991; Robinson 1995). In addition, cattle passage of TME remains pathogenic to mink when
1316 administered either orally or *via i.c.* (Marsh 1991). According to Marsh, these results suggest that
1317 the species barrier between mink and cattle may not be substantial. To protect against the
1318 possibility that TME might be transmitted to cattle, the FDA prohibits use of mink protein in
1319 ruminant feed. Mink are considered prohibited materials. The relatively small number of farmed
1320 mink, their small size, and recycling prohibitions make transmission of a prion disease from mink
1321 to cattle extremely unlikely.

1322

1323 2.3.7 Pigs

1324 There is a theoretical risk that cattle could be exposed to a TSE as the result of
1325 consuming feed supplemented with porcine-derived protein. Moreover, the fact that federal
1326 regulations classify protein from pigs as non-prohibited increases the potential for cattle to be
1327 exposed to any infectivity they may harbor.

1328

1329 There are two potential sources of this exposure: a natural TSE that infects pigs (Section
1330 2.3.7.1), and BSE-contaminated feed in the gut at the time the pig is slaughtered (Section 2.3.7.2).
1331 In practice, neither infectivity source will make a substantial contribution to cattle exposure
1332 because only a small portion of porcine-derived MBM is used as cattle feed. One reason for the
1333 limited use of porcine-derived protein in cattle feed derives in part from its price. For example, in
1334 May, 2001, the price of porcine-derived protein was \$238/ton, compared to \$177/ton for soy
1335 protein (Southern States Cooperative 2001). In addition, much rendered porcine protein is used
1336 in feed for pigs

1337

1338 The remainder of this section outlines additional factors that influence the importance of
1339 this potential source of TSE exposure among cattle. Because this source is unlikely to be
1340 significant, we do not address it quantitatively in our risk assessment (Section 3).

1341

1342

2.3.7.1 Potential Infectivity in Pigs due to TSE Infection

1343

Pigs might become infected with a TSE as the result of any of the following possibilities:

1344

1345

- The existence of a porcine-specific TSE agent;

1346

- A nonspecific TSE agent not yet adapted to pigs that has an incubation period that is longer than the life of the pig; or

1347

1348

- The spontaneous misfolding of the prion protein leading to a spontaneous TSE case in porcine.

1349

1350

1351

Consumer groups in the U.S. have expressed concern that it may be possible for a pig to

1352

become infected with a TSE. This concern stems from a 1979 incident in which one of 60 pigs

1353

presented with clinical neurologic signs, neurological degeneration, and gliosis on

1354

histopatological examination (Hansen 1999). However, further testing showed that the lesions

1355

were not pathognomonic of spongiform encephalopathy (Detwiler 2000). Moreover, the animal in

1356

question was young, a factor that is inconsistent with the TSE diagnosis. SSC (Section 4.1a in

1357

(European Union Scientific Steering Committee 1999b)) concluded that these factors argue

1358

against the presence of an unrecognized spongiform encephalopathy in pigs in the U.S.

1359

1360

Other evidence also suggests that the existence of a porcine-specific TSE agent is

1361

unlikely. No naturally occurring TSE has ever been reported in pigs (European Union Scientific

1362

Steering Committee 1999b). Moreover, pigs inoculated orally with BSE have not developed

1363

disease (European Union Scientific Steering Committee 1999b). Experimental inoculation of

1364

pigs with different strains of Kuru *via* parenteral administration did not lead to spongiform

1365

encephalopathy 52 to 76 months post inoculation (Gibbs 1979). A similar result was reported for

1366

pigs challenged with scrapie (European Union Scientific Steering Committee 1999b) up to 63

1367

months after inoculation. Pigs have also been challenged with brain material from cattle naturally

1368

infected with BSE by combined i.c., i.p., and i.v. routes (Dawson 1990). This experiment is still

1369

ongoing but preliminary results show that seven of ten pigs developed spongiform

1370

encephalopathy (Ryder 2000). Experience in the UK during the BSE outbreak, when swine had

1371

significant exposure to BSE contaminated feed, suggests that the disease did not cross the species

1372

barrier to infect pigs (MAFF (Ministry of Agriculture Fisheries and Food - now Dept for

1373

Environment Food and Rural Affairs) 2001b).

1374

1375 In an ongoing experiment in which ten pigs were subject to oral challenge with large
1376 amounts of brain from cattle naturally infected with BSE, none of the animals have developed
1377 clinical disease or neuropathologic changes. The oral challenge consisted of homogenized brain
1378 from confirmed cases of BSE. Each pig received 1.2 kg of brain divided into three doses
1379 administered at intervals of one week. Mouse bioassays of neural and non-neural tissues from
1380 pigs killed at 84 months post inoculation were initiated in October and November, 1997 and were
1381 completed in May, 2000. As of the drafting of this report, there is no evidence of residual
1382 infectivity in any of the tissues. These findings may indicate that the species barrier between pigs
1383 and cattle is higher than the species barrier between cattle and humans or between cattle and other
1384 animals that have developed spongiform encephalopathy after exposure to BSE-contaminated
1385 MBM.

1386

1387 The fact that a naturally occurring spongiform encephalopathy has never been reported in
1388 pigs may indicate that pigs are particularly resistant to this type of disease. That is, the species
1389 barrier between pigs and other species may have prevented the transmission of natural disease to
1390 pigs. For example, it is very likely that pigs in the UK were exposed to substantial doses of
1391 contaminated MBM before the implementation of the UK feed ban. Although most pigs are
1392 slaughtered at a very young age, there are a significant number of sows and boars that usually live
1393 until age four. The fact that parenterally challenged animals developed disease 17 months post
1394 inoculation suggests that these four year old animals were sufficiently old to develop disease.
1395 Other species serve as examples. Marsh et al. (1969) noted the recovery of TME from the spleen
1396 of one chicken, and from spleen, caecum, tonsils, and bursa of Fabricius after i.v. inoculation.
1397 Race and Chesebro (1998a), have shown that after inoculation of mice that either did or did not
1398 express the prion protein (PrP) gene with the hamster scrapie strain 263K, no clinical disease was
1399 produced in mice. However, infectivity found in the brain and spleen of mice expressing the
1400 prion protein was capable of causing disease in hamsters but not in mice. Hill et al. (2000), have
1401 shown the possible presence of subclinical TSE in certain animals by demonstrating that a strain
1402 of hamster prions thought to be nonpathogenic for conventional mice leads to high levels of prion
1403 replication in such mice without causing clinical disease. Alternatively, it is possible that cases in
1404 pigs in the UK have gone unnoticed.

1405

1406 Finally, even if pigs could become infected with a TSE, most are slaughtered at a young
1407 age, making it unlikely that the disease would have time to generate more than a small amount of

1408 infectivity. For example, in 1998, more than 95% of the pigs slaughtered in the U.S. were no
1409 older than six months (U.S. Department of Agriculture 1998).

1410

1411 **2.3.7.2 Potential Infectivity in Materials Consumed by Pigs**

1412 Even if pigs do not become infected with a TSE, contaminated material may be present in
1413 their digestive tract when they die. In particular, if feed administered to pigs contains cattle-
1414 derived MBM that is contaminated with BSE, pigs could harbor BSE in their alimentary tract.
1415 The following discussion outlines several factors suggesting that the potential is limited for BSE
1416 to be recycled through the guts of pigs.

1417

1418 First, most pigs are not exposed to cattle-derived MBM because there are many other
1419 economical sources of protein. For example, in the U.S., soybean meal is usually the most
1420 economical source of high quality protein available for porcine diets. It is comparable to animal
1421 proteins in terms of the quality of its amino acid components and can be used as the only protein
1422 source in most swine diets. Other sources of proteins fed to pigs include porcine MBM, peanut
1423 meal, fish meal, cottonseed meal, canola meal, sunflower meal, and raw soy beans. The amount
1424 of protein added to feed varies based on the specific needs of the animal as it grows. MBM,
1425 blood meal, and plasma can comprise between 2.5 and 5 percent of feed for pigs between
1426 weaning and 60 days of age and during the animal's growing and finishing stages. Because it is
1427 not uniformly used, it is likely that approximately 80% of the pigs grown in the United States
1428 never receive MBM.

1429

1430 Second, even among pigs that do receive cattle-derived MBM, it is likely that little if any
1431 feed would remain in the GI system at the time of processing because pigs are usually sent to
1432 slaughter after restricting feed intake for 14 to 16 hours.

1433

1434 Third, due to the high water content of the GI tract, its contents are unlikely to be
1435 rendered.

1436

1437 Finally, if the gut contents are rendered, any BSE-contaminated material that does make
1438 its way back to cattle will have gone through rendering twice, thus providing an additional
1439 opportunity for infectivity to be destroyed by this treatment.

1440

1441 **2.3.8 Poultry**

1442 Many of the same factors that make pigs an unlikely source of infectivity for cattle also
1443 make chickens an unlikely source. As a result, we do not quantitatively address this source in our
1444 risk assessment (Section 3).

1445

1446 As is the case with pigs, experimental data do not support the existence of a poultry-
1447 specific TSE. Experiments have subjected chickens to TSE challenge *via* both the parenteral and
1448 oral administration routes. The chickens challenged orally received five grams of brain from
1449 cattle confirmed to have BSE on three occasions at four, five, and six weeks of age. The chickens
1450 challenged *i.c.* received 50 µl of a 10% saline suspension of brainstem material from these cattle
1451 at one day after birth and one ml at two weeks after birth. No evidence of transmissible
1452 encephalopathy was found (European Union Scientific Steering Committee 1999b). In addition,
1453 there is no evidence to date of residual infectivity in any tissue (Detwiler 2000). Even if there
1454 were a poultry-specific TSE, the fact that chickens are typically slaughtered at an early age makes
1455 it unlikely that a prion disease would have time to develop.

1456

1457 Although chickens themselves appear to pose no substantial risk to cattle of exposure to a
1458 TSE, the use of chicken litter as a feed supplement could pose a risk (Public Citizen 2001) that
1459 should be investigated further. It is possible that cattle-derived protein feed supplements
1460 administered to chicken could contain BSE infectivity, and that BSE infectivity could pass
1461 through chicken and become available in cattle feed supplemented with chicken litter.

1462

1463 **2.3.9 Recycled Products**

1464 Several products that can be used in ruminant rations have the potential of harboring
1465 infectivity. The FDA does not exclude from ruminant feed the following products derived from
1466 mammals:

1467

- 1468 • Plate waste: Inspected and processed meat products that have been cooked and
1469 offered for human consumption and further heat processed for feed (such as plate
1470 waste and used cellulosic food casings);
- 1471 • Gelatin,
- 1472 • Milk products (milk and milk proteins),
- 1473 • Blood and blood products,

- 1474 • Tallow, grease, fat, oil
- 1475 • Aminoacids, dicalcium phosphahate, and
- 1476 • Mammalian protein, which consists entirely of porcine or equine protein.

1477

1478 **2.3.9.1 Plate Waste**

1479 Plate waste is defined to be food products that have been inspected by the FSIS or an
1480 equivalent state agency, cooked, and presented for human consumption. Plate waste often comes
1481 from large institutions, such as amusement parks or hotels. It consists of food items that have
1482 been cooked and presented for human consumption. Plate waste can undergo any of the
1483 following heat treatments: conventional rendering, extrusion and cooking at 212 °F for 30
1484 minutes (Swine Health Protection Act), pelleting at either 190 °F (internal temperature), or
1485 pelleting at temperatures similar to those of conventional rendering. This additional treatment
1486 using high temperature and pressure may further reduce the amount of infectivity that might be in
1487 this material.

1488

1489 There are approximately half a dozen processors of plate waste in the United States. The
1490 final product competes with grains in the formulation of feed, although at this time, it is not a
1491 cost-effective option because of the high processing costs.

1492

1493 Bakery products comprise approximately 90% of all plate waste going to animal feed.
1494 The remainder consists of eggs, dairy products, fish and other products of animal origin.
1495 Therefore, plate waste consists mostly of non-meat products (U.S. Food and Drug Administration
1496 1997). Because plate waste is high in moisture content, vegetable proteins must be added (50%
1497 to 60%), and it must undergo further processing to aid the dehydration and extrusion process.
1498 The best estimate is that plate waste consists of between two and four percent bovine tissue.
1499 APHIS has expressed concern that plate waste could contain infective tissue, such as brain and
1500 spinal cord (U.S. Food and Drug Administration 1997), but such tissues are unlikely to be present
1501 in any substantial quantity in plate waste.

1502

1503 We assume that high risk tissues (*i.e.*, brain) are extremely unlikely to be included in
1504 plate waste. Plate waste might contain on occasion spinal cord contamination or spinal cord in a
1505 T-bone steak. Because T-bone steaks originate from younger cattle, the likelihood of carrying
1506 infectivity at the time of slaughter is extremely low. In addition, spinal cord is unlikely to be

1507 included in the product (U.S. Food and Drug Administration 1997) because T-Bone steaks are
1508 unlikely to be included in plate waste.

1509

1510 In conclusion, current practices make the amount of infectivity in plate waste to which
1511 cattle could be exposed very small. Plate waste consists of little mammalian protein, and the
1512 tissues that are included in this waste are unlikely to contain BSE infectivity. Moreover, plate
1513 waste undergoes a substantial amount of heat treatment, which would further reduce the level of
1514 infectivity in this material.

1515

1516 **2.3.9.2 Gelatin**

1517 FDA regulations allow the feeding of gelatin to ruminants because it has not been shown
1518 to harbor infectivity. SSC considers gelatin, amino-acids, and dicalcium phosphate to be safe if
1519 processing ensures that all material is subjected to degreasing, followed by acid and/or alkaline
1520 treatment, heating to 120°C, and then heating to 138-140°C for four seconds. (European Union
1521 Scientific Steering Committee 1998b). We assume that recycling this material poses little risk of
1522 exposing cattle to BSE.

1523

1524 **2.3.9.3 Milk**

1525 FDA regulations do not prohibit the use of milk in cattle feed. No infectivity has been
1526 detected in milk or in the udder (mammary gland) of cows (as measured by the mouse bioassay)
1527 (Wells 1998). At this time, there is no evidence that any of the TSEs can be transmitted through
1528 milk.

1529

1530 SEAC considers milk to be safe and has concluded that there was no reason, following
1531 the interim results of a cohort study, to change this position (Spongiform Encephalopathy
1532 Advisory Committee 1999a; Spongiform Encephalopathy Advisory Committee 1999b). The
1533 World Health Organization has also issued a statement that concludes that milk is safe, most
1534 recently in June 2001 (WHO 2001). SEAC reviewed the processing and use of milk in the light
1535 of research implicating lymphocytes in the pathogenesis of TSEs (Spongiform Encephalopathy
1536 Advisory Committee 1999a; Spongiform Encephalopathy Advisory Committee 1999b). The
1537 Committee noted that there was no evidence of infectivity in the spleen or lymph nodes of cattle
1538 infected with BSE. In an opinion on the vertical transmission of BSE, the SSC also concluded
1539 there to be no reason to restrict the use of milk. However, SSC does recommend that as a

1540 precautionary measure, milk from BSE-affected cows be kept out of the human food supply
1541 (European Commission 1999b). We assume that recycling this material poses little risk of
1542 exposing cattle to BSE.

1543

1544 **2.3.9.4 Blood and blood products**

1545 No detectable infectivity has been found in blood or blood components of cattle infected
1546 with BSE (Wells 1998; Bradley 1999; Wells 1999; MAFF (Ministry of Agriculture Fisheries and
1547 Food - now Dept for Environment Food and Rural Affairs) 2001a). Unlike TSEs affecting other
1548 animals, infectivity has not been detected in spleen or lymph nodes of cattle experimentally
1549 infected with BSE during either the incubation period or after manifestation of clinical signs.
1550 Infectivity in blood has been found in sheep experimentally infected with BSE (Foster 1996). It
1551 is possible that in the cases of Scrapie, CWD, vCJD, and perhaps BSE in sheep, the lymphoid
1552 tissue plays an important role in the pathogenesis of the disease (Sigurdson 1999; Andreoletti
1553 2000; Ironside 2000). Some have speculated that neuroinvasion can occur directly *via* peripheral
1554 nerves or *via* the lymphoreticular system and then subsequently the peripheral nerves (Glatzel
1555 2001). Even if infectivity does exist in the blood of BSE-infected cattle, the total amount of
1556 infectivity is below the level of detection of the mouse bioassay. We assume that recycling this
1557 material poses little risk of exposing cattle to BSE. We do evaluate the potential for BSE
1558 infectivity to be present in blood as CNS micro-emboli (Section 3.1.2.3). In our sensitivity
1559 analysis, we characterize the effect of assuming inherent infectivity in blood at the level of
1560 detection (Section 3.2.2.1).

1561

1562 **2.3.9.5 Tallow**

1563 The World Health Organization has concluded that because of the proteinaceous nature
1564 of TSE agents, they will tend to remain with the cellular residues of MBM during the extraction
1565 process, rather than being extracted with the lipids of tallow (WHO 2001). In addition, a
1566 rendering study funded jointly by the EU and MAFF in 1997 showed that tallow can be
1567 considered to be safe even if its treatment does not achieve the 133°C/20 minutes/3 bars of
1568 pressure minimum treatment standard (Taylor 1997b). We assume that recycling this material
1569 poses little risk of exposing cattle to BSE.

1570

1571 **2.4 Measures Taken to Protect Against BSE**

1572 Protecting against the introduction of BSE into a country requires policies that are based
1573 on prohibitions and restrictions. Regulations mainly prohibit the import of feed, feeding
1574 materials or animals from countries with BSE, and ban recycling of ruminant materials into
1575 ruminant feed. In countries with BSE, one common risk management strategy is the removal of
1576 infected tissues from the human food supply or animal feed. Minimizing the spread of disease is
1577 complicated because BSE animals may not show clinical signs of disease for an extended period
1578 after becoming infected and the agent cannot be deactivated readily once it contaminates feed.
1579 After describing these problems (Section 2.4.1), this section discusses actions taken in the UK to
1580 address its epidemic (Section 2.4.2), actions taken in Europe to prevent the spread of BSE beyond
1581 the UK (Section 2.4.3), measures taken in the United States to prevent the introduction of BSE
1582 (Section 2.4.4), and surveillance measures in the United States (Section 2.4.5).

1583

1584 **2.4.1 General Issues Related to the Surveillance of BSE and the Deactivation of the BSE**
1585 **Agent**

1586 There is no pre-clinical or clinical test available to identify BSE in the field except when
1587 the disease is very near the end of its incubation period. Diagnosis in a live animal is based on
1588 clinical signs. Most commonly, the animal presents with changes in temperament, such as
1589 nervousness or aggression, abnormal posture, lack of coordination, difficulty in rising, or loss of
1590 body condition despite continued appetite. Specific clinical signs include abnormal head and ear
1591 position, apprehension and nervousness, apparent blindness, and exaggerated responses.

1592

1593 Microscopic examination is performed post-mortem and requires brain material
1594 preserved in formalin. This tissue is then stained and examined for the characteristic appearance
1595 of BSE specific changes. Microscopic examination is required by the EU Diagnostic Manual
1596 (European Commission 1999a; European Commission 2000) and by the Office International des
1597 Epizooties (OIE) (2000). The brain neuropathology of BSE resembles that of natural scrapie in
1598 sheep: astrogliosis, intracellular vacuolation affecting the gray matter neuropil and perikarya
1599 giving the distinctive appearance of spongiform changes, neuronal loss, and cerebral amyloidosis
1600 generally represent the most prominent changes (Wells 1991).

1601

1602 Other validated tests for postmortem diagnosis include:

1603

Section 2

- 1604 • The detection of disease-specific brain changes by electron microscopy (scrapie
1605 associated fibrils, SAF);
- 1606 • The detection of the abnormal form (PrP^{BSE}) of the host protein (PrP^c) by
1607 immunological means such as immunoblotting, immunohistochemistry (used as a
1608 confirmatory diagnoses by the EU); and
- 1609 • Detection of infectivity in tissues by bioassay (usually i.c. injection into mice).

1610

1611 Newer tests have been developed that are capable of detecting pre-clinical cases and of
1612 screening animals before slaughter. These tests have high sensitivity and specificity for detecting
1613 and confirming BSE for diagnostic purposes and can detect disease in animals not showing
1614 typical signs at slaughter (European Commission 1999a). So far, the sensitivity and specificity of
1615 the newer tests have not been shown to be better than that of immunohistochemistry at similar
1616 preclinical stages of the disease (Detwiler 2000). The tests include:

1617

- 1618 • An immunoblotting test based on the Western Blotting procedure for the detection
1619 of PrP^{Pres} using monoclonal antibody (Prionics);
- 1620 • A chemiluminescent ELISA using polyclonal anti PRP antibody for detection
1621 (Enfer); and
- 1622 • A sandwich immunoassay for PRP^{Pres} (CEA).

1623

1624 All of these tests are very rapid, with results obtained within 24 hours. Results from the
1625 Swiss surveillance system show that the Prionics test could be used to target populations other
1626 than those with clinical signs of the disease (Doherr 1999; European Commission 1999a; Schaller
1627 1999). Although these tests can detect PrP^{Pres} before the animal shows clinical signs of the
1628 disease, it is not clear at what point during the incubation period the test would reliably yield
1629 positive results. It appears that their utility is primarily near the end of the disease progression.

1630

1631 There are no commercially available methods for detecting the BSE agent in food. On
1632 the other hand, food and food products can be screened to detect high risk tissues, such as brain in
1633 sausages (European Union Scientific Steering Committee 1999a; Lucker 2000), spinal cord in
1634 ground beef (Schmidt 1999; Schmidt 2001), or Advanced Meat Recovery (AMR) product (Kelley
1635 2000; Schmidt 2001), and central nervous system tissue in the blood of animals stunned with
1636 pneumatic stunners (Garland 1996; Anil 1999; Schmidt 1999).

1637

1638 TSE agents are known for their capacity to survive severe environmental conditions such
1639 as desiccation, thermal extremes and UV exposure. Autoclaving, sodium hydroxide and sodium
1640 hypochlorite can achieve some level of inactivation but only under the most severe conditions.
1641 Currently there is no method to inactivate BSE that may be present in food for human
1642 consumption.

1643

1644 **2.4.2 Actions to Address BSE in the UK**

1645 Soon after the BSE epidemic emerged in the UK, several measures were taken to
1646 decrease the incidence of the disease in animals and the potential exposure of humans to
1647 potentially infected meat products (MAFF (Ministry of Agriculture Fisheries and Food - now
1648 Dept for Environment Food and Rural Affairs) 2000). The disease became notifiable in 1988,
1649 requiring that all cattle suspected of having BSE be destroyed and sent for diagnosis. Upon
1650 confirmation of the role of animal feed in the epidemic in 1988, the UK banned the use of MBM
1651 as an ingredient in feed produced for ruminants. In September 1990, there was a ban on the use
1652 of Specified Bovine Offals (SBO) as an ingredient in feed stuff for any species. This legislation
1653 banned from the animal feed chain tissues identified as potentially harboring the highest
1654 concentration of infectivity. This determination was made based on knowledge of the distribution
1655 of infectivity in animals infected with scrapie (Hadlow 1980; Hadlow 1982; MAFF (Ministry of
1656 Agriculture Fisheries and Food - now Dept for Environment Food and Rural Affairs) 2001c).
1657 Feed-borne BSE infections continued even after the imposition of the feed ban, but at a much
1658 lower rate (Anderson 1996). As a result of these ever more stringent bans to reduce the recycling
1659 of infectivity, the annual incidence of BSE fell by 90% between 1992 and 1997. In March 1996,
1660 the government of the UK imposed a total ban on the use of mammalian proteins in feed
1661 produced for farm animals.

1662

1663 During the first few years following the initial identification of BSE in Britain, the
1664 epidemic was primarily an animal health concern. That focus reflected the experience with
1665 scrapie, which despite its presence in the human food supply for hundreds of years, had never
1666 lead to a known case of human illness. There was some concern given knowledge of the ability
1667 of scrapie to cross species under certain circumstances and as a result, precautionary measures
1668 were put into place to protect the human food supply, including a ban on the sale of brain, spinal
1669 cord, spleen, thymus, tonsils and intestines from cattle older than 6 months (materials designated
1670 as specified bovine offal or SBO) for human consumption.

1671

1672 In 1990 a domestic cat was diagnosed as suffering from a 'scrapie-like' spongiform
1673 encephalopathy. This event generated concern that BSE also might be transmissible to other
1674 species, including humans. Scientists theorized that if BSE were transmitted to humans, it would
1675 be likely to resemble CJD and suggested that surveillance be put into place to identify atypical
1676 cases or changing patterns of the disease. In 1990 The National CJD Surveillance Unit was set up
1677 at the University of Edinburgh in response to a recommendation from the Working Party on
1678 Bovine Spongiform Encephalopathy (also known as the SouthWood Committee) (UK CJD
1679 Surveillance Unit 2003). In 1994 the Spongiform Encephalopathy Advisory Committee (SEAC)
1680 judged the risk of transmissibility to humans to be remote only because precautionary measures
1681 had been put into place.

1682

1683 In 1996 a new variant of the human Creutzfeldt-Jakob disease (now known as variant
1684 CJD or vCJD) was announced in the United Kingdom. It was identified in a small group of
1685 people, all of whom were much younger than most individuals who develop CJD (Will 1996;
1686 CJD Surveillance Unit 2001). These cases shared clinical and neuropathological features that
1687 differed from those of CJD. As of August 31, 2001, the total number of definite and probable
1688 cases of vCJD reported in the United Kingdom was 106, including 12 probable vCJD deaths for
1689 which neuropathological confirmation will never be possible (CJD Surveillance Unit 2001).
1690 Outside the UK, four vCJD cases have been reported in France, one in Ireland, and one in Hong
1691 Kong. Clinical, pathological and molecular studies provide compelling evidence that the agent
1692 that causes vCJD is the same as that which causes BSE (Collinge 1996; Will 1996; Bruce 1997;
1693 Hill 1997; Scott 1999).

1694

1695 Following the announcement by the UK government that there appeared to be a link
1696 between BSE and vCJD, several additional measures were taken to reduce human exposure to the
1697 infective agent. SEAC recommended in March, 1996 that carcasses from cattle aged over 30
1698 months be deboned and that all obvious lymphatic and nervous tissue be removed in licensed
1699 plants and that the trimmings be classified as SBO. For practical reasons, the ban was extended
1700 to apply to all material from animals more than 30 months of age. When the pathogenesis study
1701 suggested potential BSE infectivity in dorsal root ganglia, a ban on sale of bone-in-beef was
1702 introduced. The ban on retail sales of bone-in beef was lifted in 1999 following a continued
1703 decline in the incidence of BSE and the implementation of other control measures to protect
1704 against the introduction of BSE into the human food supply.

1705

1706 Among other measures introduced were the compensation of producers for the loss of
1707 animals due to regulations related to the protection of public health and the eradication of BSE.
1708 Regulations aimed at eradicating BSE included the “selective cull” (implemented in 1997), which
1709 targeted for eradication animals that were the same age as an identified BSE case from their herd.
1710 Another regulation aimed specifically at protecting human health was the so-called “over 30
1711 month scheme” (implemented in 1996), which prohibited the sale of beef from cattle over the age
1712 of thirty months for human consumption. The rationale for this ban was that cattle over the age of
1713 30 months could carry potentially substantial levels of infectivity in different tissues without
1714 having yet developed clinical signs of the disease. A complete chronology of the measures and
1715 regulations implemented in the UK following the initial outbreak of BSE in 1986 can be found at:
1716 <http://www.defra.gov.uk/animalh/bse/>.

1717

1718 **2.4.3 Actions to Address BSE in Europe**

1719 Other countries that have reported cases of BSE imported either animals or animal feed
1720 from the UK. Schreuder *et al.* (1997) discussed the risk that such imports may have posed. It is
1721 estimated that a total of 58,000 adult breeding cattle were exported from the UK between 1985
1722 and 1990. The UK also exported MBM during the years that the BSE agent is thought to have
1723 been present in rendering products from the UK. For example, because the price of MBM in
1724 England fell in 1989, exports of MBM doubled during that year (*e.g.*, 15,000 tons of MBM were
1725 exported to France alone in 1989) (Taylor 1997a).

1726

1727 Cases of BSE have been reported in several countries. Some of these cases occurred in
1728 animals directly imported from the UK or in cattle fed with feed containing UK MBM.
1729 Following export of the disease from the UK, small epidemics were observed in Northern Ireland,
1730 Switzerland, France, and Portugal, presumably caused by the rendering and feeding of material
1731 from diseased animals. Few countries in Europe have not reported any BSE cases. Because the
1732 detection of BSE depends on the characteristics of the surveillance system, the absence of a
1733 reported case does not rule out the presence of the disease.

1734

1735 Due to the potential spread of BSE to other countries, the European Union and other
1736 international organizations have taken a wide range of measures to protect human and animal

1737 health and to stop the spread of the epizootic (European Commission 2001). Some of the most
1738 important measures that have been taken by the international community include the following:

1739

1740 • The World Health Organization (WHO) in 1996 recommended that all countries
1741 ban the use of ruminant tissues in ruminant feed.

1742 • In 1996, the European Commission banned the export of British live cattle, beef,
1743 semen, embryos, and all products produced from slaughter in the United
1744 Kingdom.

1745 • The Office International des Epizzoties (OIE), the world organization for animal
1746 health, has codified the requirements for member countries to be considered BSE
1747 free. A risk assessment of the potential hazards is a pre-requisite.

1748 • Feed bans in other countries: Since 1996, many countries have started to
1749 implement feed bans.

1750 • In 2000, the Scientific Steering Committee of the EU reported the assessment of
1751 the geographical risk of BSE for 25 countries. This assessment considers the
1752 stability of the agricultural system and the likelihood of BSE occurring in the
1753 country (European Union Scientific Steering Committee 2000c).

1754 • In 2000, the European Commission adopted the decision to remove specified
1755 BSE risk materials from the feed chain and from human food.

1756 • In 2000, the European Commission prohibited the use of certain animal by-
1757 products, including MBM and blood meal (but excluding milk, or fish meal)
1758 from non-ruminants in feed for any farm animal species (effective January 1,
1759 2001).

1760 • In 2000, the European Commissions extended the SRM list to include bovine
1761 intestines.

1762 • In 2000, the European Commission adopted the decision to test all cattle over 30
1763 months of age. All animals over 30 months that cannot be tested or that test
1764 positive for BSE must be destroyed.

1765

1766 **2.4.4 Measures to Prevent the Establishment of BSE in the United States Cattle** 1767 **Population**

1768 After more than 11 years of surveillance of high-risk animals, no confirmed cases of BSE
1769 have been reported in the United States. In cooperation with the USDA FSIS, the Animal and
1770 Plant Health Inspection Services (APHIS) has taken measures in prevention, education,
1771 surveillance, and response to reduce the risk of the introduction of BSE into the U.S. cattle
1772 population.

Section 2

1773

1774 BSE became a reportable disease in the U.S. in 1986 (see Title 9 of the Code of Federal
1775 Regulations, Parts 71 and 161). As a result, USDA must be notified of suspect cases.

1776 Restrictions on imports from BSE countries have been in place since 1989, and active
1777 surveillance efforts began in 1990. As part of its surveillance effort, USDA has attempted to
1778 determine the disposition of cattle that were imported from the UK and the Republic of Ireland
1779 between 1980 and 1989. The Department continues to closely monitor the cattle in this group
1780 that have been located and are still alive.

1781

1782 In 1989, APHIS banned the import of all ruminants and restricted the import of certain
1783 cattle products from the United Kingdom and other countries where BSE was documented. In
1784 1991, APHIS restricted the import of ruminant meat and edible products and banned most
1785 byproducts of ruminant origin from countries known to have BSE in a native animal (Title 9
1786 Code of Federal Regulations, Parts 94.18 and 95.4). Countries whose products were restricted
1787 due to BSE prior to 1997 included: the UK (1989), the Republic of Ireland (1989), Switzerland
1788 (1990), Oman (1990), France (1991), and Portugal (1994). In 1997, the U.S. government
1789 prohibited the import of live ruminants and most ruminant products from all of Europe until a
1790 thorough assessment of the risks is conducted (U.S. Department of Agriculture 2003). In
1791 December, 2000, restrictions included a ban on the import of all processed animal proteins
1792 regardless the species, offal, tankage, ruminant fat, glands, processed fats and oils, and some
1793 tallow. The import restrictions in 2001 included a ban on the import of all ruminant meat, meat
1794 products and other edible ruminant products that were stored, processed or otherwise associated
1795 with a facility located in Europe or Oman. In 1990, APHIS developed a plan to respond to a BSE
1796 case in the U.S. This plan was updated by the APHIS-FSIS BSE working group in 1996.

1797

1798 FSIS performs *ante mortem* slaughter inspections at all federally inspected slaughter
1799 establishments and veterinary medical officers and food inspectors routinely evaluate animals for
1800 central nervous system disorders. Animals exhibiting suspicious CNS signs that may be
1801 indicative of BSE or any other reportable disease are withheld from slaughter. In such cases,
1802 Veterinary Services is notified. FSIS maintains a database containing information on *ante*
1803 *mortem* and *post mortem* condemnations triggered by these and other conditions.

1804

1805 The Food and Drug Administration (FDA) controls animal feed, thought to be the main
1806 exposure medium for the transmission of BSE among cattle. FDA prohibits the use of most

Section 2

1807 mammalian protein in the manufacture of animal feeds administered to ruminants (U.S. Food and
1808 Drug Administration 1997). This regulation is frequently referred to as the “feed ban.” The
1809 regulation exempts the following products: blood and blood byproducts, milk products, pure
1810 porcine and pure equine proteins, plate waste, tallow, gelatin, and non-mammalian protein
1811 (poultry, marine, vegetable). Exempted products are considered to be non-prohibited material
1812 and all other mammalian protein is considered to be prohibited material.

1813

1814 The regulation specifies procedures for those renderers, protein blenders, feed
1815 manufacturers and distributors that produce prohibited material, non-prohibited material, or both.
1816 Firms must keep records on the origin of the materials and label prohibited material “*Do not feed*
1817 *to cattle or other ruminants.*” Prohibited materials intended for export are exempt from this
1818 requirement and instead must be labeled “*For export only.*” FDA requires that renderers,
1819 blenders, feed manufacturers and distributors selling both restricted and unrestricted products
1820 ensure that the two types of proteins are kept separate throughout processing. For example, there
1821 are minimum requirements for clean-out of the production line directly after the processing of
1822 prohibited material (*e.g.*, direct cleaning and flushing) before subsequently manufactured material
1823 can be considered to be non-prohibited.

1824

1825 In early January, 2001 FDA released results of a compliance survey of 9,947 rendering
1826 and feed mills. The data demonstrated that there is significant noncompliance with the feed ban
1827 in segments of the feed industry (U.S. Food and Drug Administration 2001b). Table 2-3
1828 summarizes the results of this survey.

1829

1830
1831
1832

Table 2-3
FDA Update on Ruminant Feed (BSE) Enforcement Activities (January 10, 2001)

Practice	Proportion of Firms in Compliance		
	Renderers ^a	FDA Licensed Feed Mills ^b	Feed Mills not licensed by FDA ^c
Firms whose products were labeled with the required caution statement	84%	80%	59%
Firms with a system to prevent commingling of prohibited and non-prohibited products	72	91	74
Firms that followed record keeping regulations	96-98	98	91

1833

1834 *Notes*

1835

1836

1837

1838

1839

1840

1841

1842

1843

1844

- a For Renderers --Total number of inspections -- 239, firms handling prohibited material -- 180.*
- b. For FDA Licensed Feed Mills -- 1,240 total, inspected-- 846. Of those feed mills inspected, 347 were handling prohibited material.*
- c For Non-FDA Licensed Feed Mills -- 4,344 inspected (FDA does not know the total number because they are not required to be licensed by the Agency, but the number could be between 6,000 and 8,000). Of those feed mills inspected, 1,593 were handling prohibited material.*

1845

1846

1847

1848

1849

1850

1851

1852

1853

1854

1855

1856

1857

1858

1859

The FDA has also taken steps to reduce the risk of contaminating with BSE pharmaceuticals that contain or are produced with materials of bovine origin. These steps include the following:

- In 1992, FDA recommended the use of scrapie/BSE-free sources for materials used in dietary supplements.
- In 1993, FDA recommended that cell lines used for biologics be BSE-free.
- In 1993, FDA requested that bovine sourced materials, except gelatin, used in manufacture of regulated products be restricted to BSE-free countries.
- In 1994, FDA requested that bovine derived material for use in cosmetics and dietary supplements not be sourced from BSE countries.
- In 1996, FDA recommended the withdrawal of plasma and plasma products made from pools of persons who later developed CJD.
- In 1997, FDA requested more restrictions on the use of bovine gelatin originated from BSE countries.

1860
1861
1862

- In 1999, FDA recommended deferring the use of blood from donors with more than six months cumulative residence in the UK during the period from 1980 to 1996.

1863

1864 **2.4.5 BSE Surveillance in the United States**

1865 In addition to measures intended to mitigate the risk of BSE becoming established or
1866 propagated in the United States, the federal government has also implemented a surveillance
1867 program to help identify BSE as soon as possible if it were introduced into the U.S. Since 1986,
1868 when BSE became reportable in the U.S., USDA has encouraged the submission of brain tissue
1869 samples for testing, and has engaged in educating practitioners to look for and recognize the
1870 disease. Brain submissions are examined histologically, and immunohistochemistry has been
1871 used since 1993. USDA is considering the incorporation of rapid diagnostic tests for targeted
1872 surveillance in the future (Detwiler 2001). Between 1990 and July 2001, over 13,900 brains were
1873 examined. For each of the last six years, the rate of surveillance has been approximately double
1874 the OIE standard (OIE 2001). In 2000 and 2001, the number of brains examined was more than
1875 five times the OIE standard.

1876

1877 Animals targeted for surveillance by APHIS include cattle exhibiting signs of neurologic
1878 disease in the field (*i e.*, prior to being brought to slaughter), cattle condemned at slaughter for
1879 neurologic reasons, rabies-negative cattle submitted to public health laboratories, neurologic
1880 cases submitted to veterinary diagnostic laboratories and teaching hospitals, and a sampling of
1881 cattle that are non-ambulatory (“downer cattle”) at slaughter. Although the signs exhibited by
1882 non-ambulatory animals are generally not typical of BSE, some have suggested that these animals
1883 are a high-risk population based on anecdotal information that a TME outbreak could be linked to
1884 feeding practices involving non-ambulatory cattle (Marsh 1991). In addition, U.S. cattle
1885 inoculated *i.c.* with North American scrapie strains developed signs inconsistent with BSE signs
1886 manifest in affected animals in Europe but similar to those of non-ambulatory animals (Cutlip
1887 1994; Cutlip 1997). The APHIS surveillance approach takes into account regional differences in
1888 the movement of animals. For example, based on movement patterns, the U.S. is divided into
1889 eight regions where adult cattle would typically live and exit the production system. Based on the
1890 adult cattle populations in each region, APHIS has calculated regional surveillance goals for BSE
1891 based on international standards as if each region were an individual country.

1892

Section 2

1893 In addition to surveillance for the presence of BSE, The Centers for Disease Control and
1894 Prevention (CDC) monitors the incidence of CJD in the U.S. by analyzing death certificate
1895 information from multiple-cause-of-death data compiled by the National Center for Health
1896 Statistics. This information also is used to search for possible cases of vCJD in the U.S. As of
1897 September 2001, no such cases had been identified in the United States. Nor had any change in
1898 the incidence of CJD been observed.
1899
1900

1901 **3 Methodology**

1902 This section has four parts. Section 3.1 describes the simulation model developed as part
1903 of this analysis to quantify the impact of introducing BSE into the U.S. cattle population on both
1904 animal health and on potential human exposure to contaminated food products.

1905

1906 The description of the model in Section 3.1 reflects assumptions that are part of our “base
1907 case” scenario. This scenario represents the present state of the U.S. cattle population, along with
1908 government regulations and prevailing agricultural practices.

1909

1910 Section 3.2 describes the univariate sensitivity analysis and uncertainty analysis
1911 conducted to determine how changing various assumptions influences the model’s predictions.

1912

1913 Section 3.3 describes how we used the model, with its base case assumptions, to evaluate
1914 the impact of alternative sources of infectivity on the U.S. given current conditions. These
1915 sources include spontaneous BSE, the import of from 1 to 500 BSE-infected cattle, the import of
1916 contaminated feed, domestic scrapie, chronic wasting disease, TSEs in domestic mink, pigs, and
1917 chickens, and recycled food waste.

1918

1919 Finally, Section 3.4 evaluates alternative scenarios, including Switzerland during the
1920 period when it is thought that country first imported BSE-infected animals. That evaluation,
1921 which compares empirically reported clinical BSE cases in Switzerland during the period 1985 to
1922 2001 to the corresponding number of clinical cases predicted by the model, serves as an indicator
1923 of the model’s plausibility. Section 3.4 also describes our methodology for evaluating the
1924 possibility of spontaneous BSE in the U.S. prior to the 1997 feed ban, the impact of importing
1925 infected cattle from the UK during the 1980s, and the implementation of various risk
1926 management strategies in the U.S.

1927

1928 Unless otherwise noted, all simulation scenarios were run 5,000 times. Appendix 4
1929 discusses the numerical stability of the results.

1930

1931 **3.1 Simulation Model and Base Case Assumptions**

1932 The simulation model consists of four components, as illustrated in Figure 3-1. The first
1933 component (Section 3.1.1) characterizes the lifecycle of cattle in the U.S., quantifies the potential

1934 infection of animals at different points during this cycle, and characterizes their ultimate
1935 disposition (slaughter, death due to natural causes followed by either disposal or rendering, and
1936 death due to BSE infection followed by either disposal or rendering). The second component of
1937 the model (Section 3.1.2) describes how animals sent to slaughter are processed. Tissue may be
1938 disposed of, sent to rendering, or prepared for potential human consumption. The third
1939 component of the model (Section 3.1.3) characterizes the disposition of material sent to
1940 rendering. That material may be eliminated from further consideration (*e.g.*, because it will be
1941 disposed of, exported, or used to produce feed for animals other than cattle) or end up in feed that
1942 is administered to cattle. The final component of the model (Section 3.1.4) quantifies infectivity
1943 in food available for potential human consumption.

1944

1945 Detailed information on the parameters described in this section appears in Appendix 1.
1946 As described in that appendix, each parameter is defined as a table (although it may be a table
1947 containing only a single entry). These tables, in turn, are grouped into files. In our discussion
1948 below, we identify the name of the parameter table and the name of the file containing that table
1949 for each assumption discussed.

1950

1951 **3.1.1 Cattle Population Dynamics**

1952 Figure 3-2 further details the cattle population dynamics component of the simulation
1953 model. In particular, this component describes the rate at which cattle are born, the rate at which
1954 animals are slaughtered, and the rate at which they die of other causes. Cattle can become
1955 infected when they are born as a result of maternal transmission. Alternatively, they can be born
1956 uninfected but become infected later as a result of exposure to BSE-contaminated feed. Infected
1957 animals may proceed to the clinical stage of the disease. Alternatively, they may be slaughtered,
1958 or die of other causes before that happens. Likewise, animals displaying clinical signs may also
1959 be slaughtered or die of other causes, including BSE. Section 3.3 details the different ways in
1960 which BSE infectivity could be introduced into the U.S. cattle population.

1961

1962 The model includes a detailed characterization of the cattle population dynamics because
1963 many of the rates influencing disease prevalence depend on animal age, type, and gender. Rates
1964 depending on at least some of these factors include the rate at which healthy animals become
1965 infected due to consumption of contaminated feed (this dependence stems from the influence of
1966 age, type, and gender on the amount of meat and bone meal (MBM) animals consume, and the

1967 influence of age on susceptibility to infection given a specified exposure), the rate at which
1968 animals are slaughtered, and the rate at which animals die of causes other than slaughter.

1969

1970 The remainder of this section summarizes the following base case assumptions: 1) the
1971 number of animals in the U.S. cattle population by age, gender, and type (*i.e.*, dairy or beef,
1972 destined for production or breeding), their birth rate, slaughter rate, and rate of death from other
1973 causes; 2) cattle consumption of bypass protein and blood meal by age, type, and gender; 3) the
1974 dose-response relationship for cattle orally exposed to BSE and the influence of age on this
1975 relationship; 4) the rate at which infected cows transmit BSE to their offspring; and 5) the
1976 incubation period for BSE (*i.e.*, the time between infection and the appearance of clinical signs)
1977 and the time until death following the development of clinical signs.

1978

1979 **3.1.1.1 Size of Cattle Population, Birth Rates, Slaughter Rates, and Rates of Death**
1980 **due to Other Causes**

1981 The simulation developed for this analysis requires specification of the number of
1982 animals by age in months for each gender within each of three animal types: dairy, beef, and beef
1983 reproductive animals. This last group represents those beef cattle that live beyond the age of 24
1984 months for the purpose of providing beef calves. Base case values for the cattle population size
1985 appear in the <initsize> table of the genesisVisitor file (see Appendix 1).

1986

1987 Developing this information was complicated because available data sources do not break
1988 down the age distribution for cattle in sufficient detail, and in some cases, combine groups that
1989 must be characterized separately for the simulation. For example, statistics published by the FSIS
1990 Animal Disposition Reporting System (ADRS) (U.S. Department of Agriculture 1998) report the
1991 slaughter rate for dairy and beef cows combined, rather than specifying the slaughter rate for each
1992 group separately. The development of this information has been further complicated because
1993 some of the reported statistics do not appear to be consistent with each other. For example, as
1994 explained below, the reported number of steers and heifers slaughtered is consistent with birth
1995 rates that imply a total cattle population of approximately 140 million, rather than the true value
1996 of approximately 100 million.

1997

1998 When forced to diverge from reported statistics for the purpose of maintaining internal
1999 consistency, we do so in ways that minimize the impact of distortions on the validity of the
2000 simulation results. In the example described in the preceding paragraph, our inflation of the U.S.

Section 3

2001 cattle population should have a minimal impact on simulation results because the model-predicted
2002 rate at which BSE spreads does not in general depend on this statistic³. In particular, the assumed
2003 proportion of animals of each type (beef, dairy, or beef reproductive), gender, and age influences
2004 the probability of exposure to recycled protein. Because this relationship depends only on the
2005 relative size of the different cattle groups, scaling their size by a constant factor does not
2006 influence the simulation's results.

2007

2008 *Population size*

2009

2010 The specific population values for each type/gender/age category were computed using
2011 spreadsheet software and the birth, death, and slaughter rates described in this section. The
2012 documentation in Appendix I (file genesisVisitor, table <initSize>) describes these computations.
2013 However, although each simulation begins with the population distribution specified in Appendix
2014 I, the model alters these values to reflect the simulated impact of birth, death, and slaughter. As a
2015 result of these influences, the initial population of approximately 140 million decreases to and
2016 stabilizes at approximately 130 million during execution of the simulation. As noted above, this
2017 change has a very limited impact on the simulation results.

2018

2019 *Slaughter Rate*

2020

2021 Animals are removed from the cattle population for slaughter at different rates depending
2022 on type, gender, and age. Dairy cows are culled as they age primarily when their reproductive
2023 and production capacity become inadequate. The base case assumptions for the slaughter rates
2024 are based on statistics recorded by USDA and are detailed in the <rateSlaughter> table, which is
2025 located in the rateSlaughter file (see Appendix 1).

2026

2027 *Death Rate for Reasons Other Than Slaughter*

2028

2029 The so-called "natural death rate" may be potentially important because some fraction of
2030 these animals, also referred to as animals that "die on the farm," are sent to rendering. Animals
2031 that die on the farm due to BSE infection have the maximum level of infectivity and therefore
2032 introduce the possibility that a substantial amount of BSE contamination could contaminate

³ The possibility of spontaneous development of BSE is the one exception to this generalization because its rate is proportional to the size of the population. By overstating the size of the population, we have therefore overstated the

2033 rendered products. The base case assumes that animals with BSE will live only 2 to 6 months
2034 after reaching the clinical stage of the disease. The natural death rates assumed by the base case
2035 are specified in the <probDeath> table, which is located in the deathVisitor file (see Appendix 1).
2036

2036

2037 *Birth rate assumptions*

2038

2039 The base case assumes that female cattle can calve between the ages of 24 and 180
2040 months. During that time, they produce a calf once every 12 months on average. Documentation
2041 accompanying the discussion of the birthVisitor file (see Appendix 1) explains the basis for these
2042 assumptions.
2043

2043

2044 **3.1.1.2 Proportion of Animals That Die on Farm that Are Rendered**

2045 The base case assumes that 85% of the animals that die on the farm (*i.e.*, before they are
2046 sent to slaughter) are rendered. This assumption is specified by parameter table <farmdeathdisp>
2047 in parameter file misc.
2048

2048

2049 **3.1.1.3 Cattle Consumption of Bypass protein and Blood Meal**

2050 MBM is one supplement for livestock feed, although in the U.S., other sources are also
2051 used, especially vegetable protein derived primarily from soybeans. The primary hypothesis for
2052 the spread of BSE in the UK is that infectious materials was recycled through the rendering and
2053 feed production processes resulting in the subsequent exposure of cattle. The amount of bypass
2054 protein-supplemented feed consumed by an animal, and hence its potential exposure to MBM,
2055 depends on the animal's type, gender, and age. Dairy cows receive the greatest amounts of
2056 supplemental bypass protein. Because the base case assumes that there may be breaches of the
2057 FDA feed ban (Section 3.1.3), some exposure can occur as the result of exposure to feed if BSE is
2058 present in the U.S. The <consumption> tables in files proteinInfector and bloodInfector
2059 respectively detail our assumptions for cattle consumption of bypass protein and blood meal.
2060

2060

2061 **3.1.1.4 BSE Dose-Response**

2062 The dose-response function for BSE quantifies the probability that an exposed animal
2063 will become infected with BSE as the result of ingesting contaminated materials. The dose is

potential impact of spontaneous disease, should it exist (see Section 3.4.2 in this report).

2064 quantified in terms of the number of susceptibility-adjusted ID₅₀s ingested. The susceptibility-
2065 adjusted ID₅₀ dose equals the product of an age-specific susceptibility factor and the number of
2066 unadjusted ID₅₀s ingested. The base case assumes that the dose response is linear up to an
2067 exposure level of 2.0 susceptibility-adjusted ID₅₀s, with an infection probability of zero at an
2068 exposure level of zero, and an infection probability of 1.0 at an exposure level of 2.0 adjusted
2069 ID₅₀s. For example, an animal that ingests 1.0 susceptibility-adjusted ID₅₀s has a 50% chance of
2070 becoming infected. Note that an animal that ingests more than 2.0 adjusted ID₅₀s has a 100%
2071 chance of becoming infected. Figure 3-3 illustrates the straight-line dose-response relationship
2072 assumed as part of the base case, along with a hypothetical alternative sigmoidal dose-response
2073 relationship. The dose-response relationship is specified by table <probInfection> in the
2074 proteinInfector file.

2075

2076 Our relationship between susceptibility and age (see Figure 3-4) is based on the
2077 assumption that susceptibility peaks at age four months and that it declines exponentially
2078 thereafter at a rate of 85% per year, leveling off at approximately 10% of its peak value (de
2079 Koeijer 1999). Table <susceptibility> in file proteinInfector (see Appendix 1) details this
2080 relationship. Section 2 provides further background on susceptibility.

2081

2082 **3.1.1.5 Maternal Transmission**

2083 Although there is no direct evidence of BSE transmission from cow to calf, it is assumed
2084 to have occurred when a calf born to a cow incubating BSE contracts the disease in the absence of
2085 any other known sources of BSE exposure. Section 2.2.1 reviews evidence of maternal
2086 transmission for other TSEs, with the best evidence from scrapie (Kimberlin 1990; Foster 1992;
2087 Elsen 1999), and for BSE (Donnelly 1997a; Donnelly 1997b; Ferguson 1997a; Wilesmith 1997;
2088 Donnelly 1998). The base case assumes that calves born to infected cows during the last one-
2089 sixth of the incubation period will become infected with 10% probability. Text accompanying
2090 table <maternalContagiousPoint> in file sickBovine and table <probTrans> in file birthVisitor
2091 (see Appendix 1) further documents the basis for these two parameter values.

2092

2093 **3.1.1.6 BSE Incubation Period, and Time Until Death Following Onset of Clinical** 2094 **Signs**

2095 The base case assumes that the duration between infection and manifestation of clinical
2096 signs follows a distribution inferred by Ferguson *et al.* (1997b) from data collected in the UK.

2097 The density is right-skewed with a median of approximately four years. The 5th percentile is
2098 approximately 2.5 years, the median is approximately four years, and the 95th percentile is
2099 approximately seven years. Table <clinicalDate> in file sickBovine (see Appendix 1) further
2100 details this distribution.

2101

2102 The base case assumes that the time between the manifestation of clinical signs and death
2103 is uniformly distributed between 2 and 6 months (Heim 2001). Table <clinicalDuration> in file
2104 sickBovine (see Appendix 1) documents this assumption.

2105

2106 **3.1.2 The Slaughter Process**

2107 If an animal with BSE is slaughtered, some practices can contaminate tissues destined for
2108 potential human consumption with BSE infectivity. In addition, many tissues not used for human
2109 consumption go to rendering and may become available to infect other bovines (Section 3.1.3).
2110 This section describes the base case assumptions for the slaughter process (Figure 3-5). It also
2111 describes ways in which infectivity can be diverted from uses that may result in either human or
2112 bovine exposure.

2113

2114 **3.1.2.1 Level of Infectivity and Distribution of Infectivity Throughout the Carcass**

2115 The amount of infectivity that becomes available for human consumption or ends up
2116 being recycled into cattle feed depends in part on the total amount of infectivity in a slaughtered
2117 animal and how that infectivity is distributed through its carcass. Our model assumes these
2118 factors depend on the amount of time that has passed since the slaughtered animal became
2119 infected. Tables <organDistribution> and <totalInfectivity> in file materializer (see Appendix 1)
2120 details our base case assumptions.

2121

2122 Our description of the distribution of infectivity among the tissues of an infected animal
2123 is based on results from the pathogenesis experiment (Wells 1998; Wells 1999), as interpreted by
2124 SEAC (February, 1998). This experiment measured the infectivity in each of 44 tissues and
2125 fluids following experimental infection of cattle with BSE. The experiment found infectivity in
2126 the small intestine from months 6 to 18 months post infection, with no detectable infectivity in
2127 any other tissues. At the end stage of disease, (≥ 32 months post infection), infectivity was found
2128 in the brain, spinal cord, dorsal root ganglia (DRG), trigeminal ganglia (TGG), and again in the
2129 small intestine. We assume that findings of infectivity in bone marrow at one time point were

2130 spurious, although we do investigate the potential for the disease to directly infect blood (so-
2131 called “inherent infectivity”) (Section 3.2.2.1). Table 3-1 details our specific assumptions.

2132

2133 Note that these assumptions are based on an assumed incubation period of 36 months (as
2134 observed in the pathogenesis study). For animals with incubation periods of durations other than
2135 36 months, the time periods post inoculation are scaled accordingly. For example, for an animal
2136 with an incubation period of 72 months, there is no infectivity in the brain prior to month 64 (*i.e.*,
2137 $32 \times 72 / 36$).

2138

2139

2140 **Table 3-1**
2141 **Relative Infectivity of Specific Tissues Specified From an Infected Bovine**
2142 **(Based on (European Union Scientific Steering Committee 1999a))^a**

2142

Tissue	Fraction of Total Infectivity
Brain	No infectivity in cattle < 32 months post-inoculation (PI) 32 months PI and over: 64.1%
Trigeminal Ganglia	No infectivity in cattle < 32 months post-inoculation. 32 months PI and over: 2.6%
Other Head (eyes)	No infectivity in cattle < 32 months post-inoculation. 32 months PI and over: 0.04%
Distal Ileum	6-18 months post inoculation: 100% 18-31: No Infectivity 32 months PI and over 3.3%
Spinal Cord	No infectivity in cattle < 32 months post-inoculation. 32 months PI and over: 25.6% infectivity
Dorsal Root Ganglia	No infectivity in cattle < 32 months post-inoculation. 32 months PI and over: 3.8 % infectivity

2143

2144 Notes:

2145

2146

2147

2148

a. *The post-inoculation time values in this table reflect the assumption that the incubation period is 36 months. See text for explanation.*

2149

2150

2151

2152

2153

The base case assumes that the total quantity of infectivity in an animal with BSE reaches its maximum level when the animal develops clinically detectable signs (*i.e.*, becomes “clinical”) (see Section 3.1.1.6 for a discussion of the incubation period duration). Prior to that time, the total level of infectivity follows the pattern illustrated in Figure 3-6. The example in Figure 3-6 corresponds to the case in which the animal develops clinical signs 36 months after infection.

2154 During the first five months of infection, total infectivity in the animal is around 0.1% of its
2155 maximum value, followed by an increase to around 2.5% of its maximum value between months
2156 6 and 18 post infection. Up until this point, all infectivity is assumed to be in the gut. Starting in
2157 month 19, infectivity is assumed to be distributed among several tissues, with the bulk in the
2158 brain and the spinal cord, and the remainder divided among the gut, DRG, eyes, and TGG. At
2159 this time, total infectivity drops to zero but and then grows exponentially until it reaches its
2160 maximum level in month 36. For incubation periods other than 36 months, the model scales the
2161 horizontal (time) axis in Figure 3-6 proportionally. The total amount of infectivity in an animal
2162 with clinical BSE is assumed to 10,000 cattle oral ID₅₀s (European Union Scientific Steering
2163 Committee 1999a; Spongiform Encephalopathy Advisory Committee 2000; Gale 2001). Note
2164 that this value has not been adjusted to reflect age-specific susceptibility (see Section 3.1.1.4 and
2165 Appendix 1, Section 2.3.4).

2166

2167 **3.1.2.2 *Antemortem* Inspection**

2168 Once the animal is at the slaughter facility, it is inspected for signs of disease. FSIS
2169 regulations require that for certain diseases, the whole animal is condemned at *antemortem* (AM)
2170 inspection (U.S. Department of Agriculture 1997). Condemned animals can be rendered or
2171 incinerated.

2172

2173 Animals not showing clinical signs at AM inspection are not likely to be condemned for
2174 BSE but could be condemned if they show signs of other diseases. The condemnation rates for
2175 animals not showing clinical BSE signs depend on age and gender. The rates used in the base
2176 case are based on data collected by FSIS for the year 1998 (see Table 3-2). In particular, the base
2177 case assumes that the AM condemnation rate is approximately 1% for animals less than one year
2178 of age, 0.01% for animals between the ages of one year and 31 months, and 0.2% for animals
2179 older than 31 months of age.

2180

2181
2182
2183

**Table 3-2
Cattle Slaughtered and Condemned (1998)^a**

Cattle age group	Total Animals slaughtered	Total Animals Condemned	Probability not pass AM	Animals Condemned Postmortem	Probability that will not pass Postmortem
< 12 months	1,483,430	14859	0.0098	13,799	0.0092
12 to 24 months	32,690,003	2,349	0.0001	22,697	0.0007
≥ 24 months	7,815,074	21,906	0.0028	11,0172	0.0139

2184

2185

Notes.

2186

2187

a. Data from USDA's Animal Disposition Reporting System (U.S. Department of Agriculture 1998)

2188

2189

Animals that are condemned following AM inspection are usually rendered, although a small proportion are incinerated. The base case assumes that 98% of condemned animals are rendered and that the rest are incinerated. The likelihood that an animal condemned at AM inspection is rendered or incinerated is assumed to be independent of its BSE status. The means of disposal is important because animals that are incinerated cannot contaminate human food or animal feed.

2195

2196

Animals that do manifest the clinical signs of BSE can be identified by AM inspectors. It also is possible that farmers might hold back from slaughter animals with BSE signs to prevent the case from being discovered. It is difficult to estimate how effectively U.S. inspectors would detect an animal with BSE signs because the disease has not been detected in this country. The USDA has conducted training for inspectors to make them aware of these signs. The effectiveness of inspectors at detecting other CNS diseases could conceivably be used to estimate how effective they would be at detecting animals with clinical signs of BSE. In practice, however, the prevalence rate for these other diseases are often unknown. Our base case assumes that clinical BSE cases would be detected at AM inspection 90% of the time (see table <probPassAM> in file AMInspector). Because this value is highly uncertain, our uncertainty analysis evaluates the impact of using a wide range of values on the results of our simulation (see Section 3.2.2).

2208

2209

3.1.2.3 Stunning

2210

Stunning humanely renders animals unconscious for slaughter. It is usually performed by mechanical devices, most commonly captive bolts that may or may not penetrate the skull. One

2211

2212 type of penetrating captive bolt is referred to as an “air-injected pneumatic stunner” because it
2213 injects a jet of air into the brain at the end of the cylinder stroke. Stunners that use air injection
2214 can deposit CNS tissue emboli in blood, heart, lung, and liver. Malfunctions in these devices
2215 both increase the probability that emboli will be created and the amount of emboli that will be
2216 deposited. However, based on our conversations with USDA personnel (in headquarters and in
2217 the field), individuals in the beef packing industry, and others, the base case assumes that air-
2218 injected stunning is not currently used in the U.S. cattle industry (see parameter table
2219 <probType> in file stunner). Other scenarios evaluating past practices do assume the use of air-
2220 injected pneumatic stunning (see Section 3.2.2).

2221

2222 There also is some concern that other stunning methods may produce CNS micro-emboli
2223 that could contaminate blood (European Union Scientific Steering Committee 2000e). The base
2224 case assumes that stunners not using air injection can create very small emboli that are found only
2225 in blood (see parameter table <emboli> in file stunner). The amount of emboli in the blood is not
2226 affected by whether the stunner malfunctions.

2227

2228 **3.1.2.4 Exsanguination**

2229 Following stunning, animals are bled. Bovine blood can be processed for human
2230 consumption, processed to make blood meal that can be used in ruminant feed, rendered, or
2231 disposed of. The base case assumes that 15% of blood is made into blood meal that has the
2232 potential to be used in cattle feed (parameter table <probDestination in file feedTransporter). The
2233 base case also assumes that blood collected for human consumption is not contaminated with
2234 emboli.

2235

2236 Blood collected to produce meal for animal consumption may become contaminated with
2237 CNS tissue if some of that tissue drips from the hole created by the stunner. The base case
2238 assumes that air-injected pneumatic stunners generate this type of contamination with 30%
2239 probability (see parameter table <probDrip> in file stunner), and that when this contamination
2240 does occur, 4% of the infectivity in the brain ends up in the blood being collected (parameter
2241 table <fracDrip> in file stunner). The base case assumes that stunners that do not use air injection
2242 never cause this type of contamination.

2243

2244 **3.1.2.5 Disposition of Brain**

2245 Following exsanguination, the head is removed from the carcass. USDA has mandated
2246 inspection of some parts of the head that are collected for human consumption (*e.g.*, tongue).
2247 Because brain is the tissue with the greatest amount of infectivity in an animal with advanced
2248 BSE, the disposition of the head is important. There are no available data on the fraction of
2249 brains collected for sale as human food. The base case assumes that 1% of the brains are
2250 removed for potential human consumption in the U.S. and that the rest are rendered (see
2251 parameter table <probPassFood> in file foodInspector). Section 3.2.2.5 lists base case and worst
2252 case assumptions for other tissues.

2253

2254 **3.1.2.6 Splitting and Aerosolization**

2255 After removal of the head, the carcass is split longitudinally with a saw to facilitate
2256 handling and further processing. When the carcass is split some spinal cord is aerosolized and
2257 can contaminate edible meat. Based on data from experiments that measured the amount of
2258 spinal cord associated protein deposited on the carcass during splitting (Harbour 2001), the base
2259 case assumes that approximately 0.001% (2.5 mg) of the spinal cord contaminates edible meat.
2260 The base case further assumes that additional carcass treatments, like washing and steaming, do
2261 not reduce the amount of contamination. Text accompanying table <fracAerosol> in file splitter
2262 (see Appendix 1) documents this assumption.

2263

2264 **3.1.2.7 Disposition of the Spinal Cord and Dorsal Root Ganglia**

2265 The vertebrae of the animal are arranged in a column that houses and protects the spinal
2266 canal. Because spinal cord and the dorsal root ganglia (DRG), which are nerve ends emerging
2267 from the spinal cord, can contain BSE infectivity, their disposition influences the extent to which
2268 meat recovered for human consumption may become contaminated. The magnitude of this
2269 contamination and which selections of meat become contaminated depend on whether a mis-split
2270 occurs, whether the slaughter plant uses advanced meat recovery (AMR), and whether it removes
2271 the spinal cord from the carcass. The extent to which AMR product becomes contaminated is
2272 particularly sensitive to mis-splits because they can leave behind pieces of spinal cord
2273 encapsulated in the vertebral column that are processed by AMR. This section first discusses the
2274 frequency of mis-splits, the proportion of carcasses processed using AMR, and the proportion

2275 from which the spinal cord is removed. Finally, it discusses how mis-splitting, AMR, and spinal
2276 cord removal influences contamination.

2277

2278 *Mis-split frequency*

2279

2280 Mis-splitting refers to the incomplete cutting of the spinal column with a saw. A mis-
2281 split occurs when the cut veers off the vertical and terminates at a point short of the cervical
2282 vertebrae (carcasses are split caudal to cranial). The likelihood that mis-splitting will occur
2283 depends on the size and age of the animal (*e.g.*, calves are more likely to be mis-split than bulls or
2284 cows) and the proficiency of the saw operator. The rate and extent of mis-splitting influences the
2285 potential for spinal cord from an infected animal to contaminate human food, primarily in the
2286 Advanced Meat Recovery process (Section 3.1.2.8). The base case assumes that among animals
2287 below the age of 24 months, mis-splits occur 5% of the time, whereas for older animals, mis-
2288 splits occur 8% of the time. Table <probMS_AMR_SCRemove> in file splitter (see Appendix 1)
2289 details estimates for the rate and extent of mis-splits.

2290

2291 *The proportion of cattle processed using AMR*

2292

2293 Once the carcass is split, the disposition of the spinal cord depends on whether or not the
2294 slaughter facility processes the vertebrae using advanced meat recovery (AMR). AMR machines
2295 process bones to recover meat remaining after the hand deboning process is completed. USDA
2296 rules allow the AMR product to be labeled as “meat”. Approximately 70% of fed cattle and 60%
2297 of cows are processed in facilities that use AMR (Sparks Companies 1999). The base case
2298 assumes that AMR is used to process no animals below the age of 12 months, 65% of animals
2299 between the ages of 12 and 23 months, and 60% of animals 24 months of age or older. Table
2300 <probMS_AMR_SCRemove> in file splitter (see Appendix 1) details estimates for the proportion
2301 of material processed using AMR.

2302

2303 *Spinal cord removal – Plants that use AMR*

2304

2305 An FSIS directive requires that the spinal cord be removed from the vertebral column
2306 before the backbones enter the AMR process. The base case assumes that spinal cords are
2307 removed with 98% probability in plants using AMR. Spinal cords removed in this manner are
2308 rendered. In the event that spinal cord is not removed prior to AMR, it can contaminate the AMR

2309 product, although the probability of this occurring is small. In addition, if the carcass is mis-split,
2310 the spinal cord that remains encapsulated in the spinal canal (usually a small portion of the spinal
2311 cord) contaminates AMR product unless it is removed by facility personnel. Whether an AMR
2312 processing system is used depends on the size and age of the animal (e.g., calves are not likely to
2313 go through AMR). The amount of spinal cord left behind that can contaminate edible meat also
2314 depends on the age and type of the animal (e.g., for steers and heifers, the lumbar area does not
2315 go through AMR because T-bone steaks are more profitable). Table
2316 <probMS_AMR_SCRemove> in file splitter (see Appendix 1) details estimates for the proportion
2317 of spinal cords that are removed.

2318

2319 *Spinal cord Removal – Plants that do not use AMR*

2320

2321 If a facility does not use AMR, FSIS does not require removal of the spinal cord from the
2322 carcass. However, some slaughterhouses choose to remove it and send it to rendering. The base
2323 case assumes that spinal cords are removed with 50% probability in plants that do not use AMR.
2324 If the spinal cord is not removed, it remains in certain cuts of beef and is hence available for
2325 potential human consumption (e.g., T-bone steak). In addition, spinal cord left in the carcass can
2326 contaminate the boning table. Finally, a small fraction of the spinal cords removed from steers
2327 and heifers are destined for human consumption. Table <probMS_AMR_SCRemove> in file
2328 splitter (see Appendix 1) details estimates for the proportion of spinal cords that are removed.

2329

2330 *Fraction of spinal cord and DRG that contaminate meat recovered for human*
2331 *consumption*

2332

2333 The DRG are firmly attached to the bones of the spinal column and are not removed even
2334 if the spinal cord is removed. The disposition of the DRG depends on the cuts of beef recovered
2335 for human consumption (which depend on the age of the animal) and on the use of AMR
2336 processing systems. For example, some cuts of meat from young animals, such as steers and
2337 heifers, might be sold with the vertebrae attached (e.g., T-bone steaks), and in those particular
2338 circumstances DRG can reach the consumer. However, it is important to note that even if DRG
2339 reaches the consumer, it is unlikely to be consumed unless the bone is aggressively cleaned. In
2340 other regions of the vertebral column, DRG will remain attached to the bone because they are
2341 unlikely to be removed by standard deboning operations. The vertebrae and DRG from young
2342 animals are likely to be rendered. For older animals (e.g., bulls and cows) that are deboned by
2343 hand, DRG will not reach the consumer and will instead be rendered.

2344

2345 If the spinal column is processed using AMR, the DRG are likely to contaminate the
2346 AMR product. For young animals, only a fraction of the vertebral column and DRG will be
2347 processed using AMR because parts of the backbone are contained in high value bone-in cuts of
2348 meat. For older animals, such as bulls or cows, all vertebrae are likely to be processed using
2349 AMR. If the facility does not process the spinal column using AMR, other technology, such as
2350 vibration or hand held knives (*e.g.*, Whizzard knives), are used to recover the remaining meat
2351 attached to the bones. Because of the location of the DRG and the presentation of the backbones
2352 on the boning table, these knives are unlikely to contaminate meat or ground beef with DRG or
2353 spinal cord.

2354

2355 Tables $\langle \text{fracDRGInMuscle} \rangle$, $\langle \text{fracDRGInAMRMeat} \rangle$, and $\langle \text{fracDRGInBone} \rangle$ in file
2356 splitter (see Appendix 1) detail the fraction of the infectivity in DRG that ends up contaminating
2357 muscle, AMR product, or remains connected to the bone, respectively. These values depend on
2358 whether a mis-split occurs, the use of AMR, and on whether the spinal cord is removed. Tables
2359 $\langle \text{fracSCInMuscle} \rangle$, $\langle \text{fracSCInAMRMeat} \rangle$, and $\langle \text{fracSCInBone} \rangle$ in file splitter (see Appendix 1)
2360 provide the corresponding assumptions for spinal cord contamination.

2361

2362

3.1.2.8 Postmortem Inspection

2363 Organs and tissues from cattle passing AM inspection are inspected *postmortem* (PM) to
2364 ensure fitness for human consumption. FSIS regulations require that the whole animal be
2365 condemned when certain diseases are suspected, while for other diseases and conditions, only
2366 some tissues are excluded from use in human food. There are no visible characteristics of BSE
2367 cattle that can be detected at PM inspection. Nevertheless, the base case assumes that some
2368 infected animals or tissues from animals with BSE are condemned at PM inspection for reasons
2369 other than the presence of BSE. These condemnation rates have been measured and reported by
2370 FSIS (Table 3-2). The FSIS data specify rates by age and gender. The base case rates appear in
2371 Table $\langle \text{probPassPM} \rangle$ in file PMInspector (see Appendix 1).

2372

2373

3.1.2.9 Recovery of Material for Potential Human Consumption

2374 After the carcass is split, meat for potential human consumption is recovered. Some
2375 potentially infectious tissues may be purposely recovered for potential human consumption. The
2376 base case assumptions for the proportion of various tissues recovered for this purpose are detailed

2377 in Table <probPassFood> in file foodInspector. Not all tissue that is potentially available for
2378 potential human exposure is actually consumed. Rates of waste during distribution and in the
2379 home, portion sizes, and other factors will influence actual human exposure. Section 3.1.4
2380 describes the basis for these assumptions.

2381

2382 **3.1.3 Rendering and Feed Production**

2383 Rendering is a process that recovers useful materials like fat, tallow, and protein, by
2384 cooking the animal remains, separating the products, and by further processing and purifying the
2385 resulting meat and bone meal (MBM). MBM is a rendering product rich in protein that can be
2386 used as a feed supplement, among other uses. If the remains of an infected animal, including
2387 either a sheep with scrapie or a bovine with BSE, are made into MBM that is then fed to cattle,
2388 additional animals could become infected. Current regulations in the U.S. (U.S. Food and Drug
2389 Administration 1997) prohibit the feeding of mammalian derived protein to other ruminants with
2390 some exemptions. The feed ban does not restrict the use in ruminant feed of porcine protein,
2391 equine protein, ruminant blood, ruminant milk, plate waste, or gelatin. Other sources of protein,
2392 primarily of vegetable origin (*e.g.*, soy), are also widely used to supplement livestock rations.
2393 The extent of compliance with the feed ban in rendering and feed formulation influences the
2394 extent of possible cattle exposure to infectivity from a rendered diseased animal. Infectivity can
2395 also be eliminated as a result of using ruminant derived materials in ways that do not lead to any
2396 potential exposure among U.S. cattle (*e.g.*, export). Figure 3-7 illustrates our characterization of
2397 how materials flow through rendering plants, feed formulation plants, and to the farm.

2398

2399 **3.1.3.1 Rendering Inactivation**

2400 Rendering may reduce the amount of BSE infectivity in material by subjecting it to heat
2401 and pressure. Different rendering systems (*e.g.*, continuous, batch, and vacuum) inactivate BSE
2402 or scrapie infectivity to different degrees (Taylor 1995; Taylor 1997b; Schreuder 1998). Table 3-
2403 3 quantifies the base case assumptions for the reduction in infectivity achieved by each
2404 technology and the proportion of animals rendered using each technology. The sensitivity
2405 analysis varies these proportions and the degree of inactivation achieved. The text in Appendix 1
2406 accompanying table <renderFactor> in file renderer further documents these assumptions.

2407

2408
2409
2410
2411

Table 3-3
Infectivity inactivation achieved and proportion of cattle processed by different types of rendering systems

Technology	Infectivity Inactivation Achieved (log base 10)	Proportion of cattle rendered
Batch	3.1 logs	5%
Continuous/fat added	2 logs	45%
Continuous/ no fat added	1 log	45%
Vacuum	0 logs	5%

2412

2413

3.1.3.2 Meat and Bone Meal Production

2414

2415

2416

2417

2418

2419

2420

2421

2422

2423

2424

U.S. regulations recognize three types of rendering facilities, designated here as nonprohibited, prohibited, and mixed. A nonprohibited plant processes only porcine, equine or poultry (nonruminant species) and produces animal-based protein products that can be used legally in cattle feed. A prohibited rendering plant may process ruminant or mink raw materials, along with other sources of animal protein, and produces prohibited MBM that may not be used in cattle feed. Mixed plants produce both nonprohibited and prohibited MBM. These plants must use separate production lines or a common line with specified cleanout procedures. The base case assumes that 94.9999% of cattle remains are sent to prohibited rendering plants, 5% are sent to mixed plants, and 0.0001% are sent (incorrectly) to non-prohibited plants (see Table <probType> in file renderer)..

2425

2426

2427

2428

2429

2430

2431

2432

2433

2434

2435

2436

2437

2438

The base case assumes that cattle infectivity can reach bovines in several ways. Material from a prohibited rendering plant could be mislabeled and used in the formulation of cattle feed. Mislabeling could also occur in a mixed plant. A mixed plant could contaminate non-prohibited MBM by using incorrect source material or by failing to completely flush and clean shared processing machinery. A nonprohibited plant might contaminate their MBM by using prohibited source material although this is unlikely. Even if non-prohibited MBM is contaminated, the potential for bovine exposure is reduced because much of this MBM goes to uses other than cattle feed.

Table 3-4 describes the disposition of MBM infectivity based on the flow shown on Figure 3-7. Tables <probContaminate> and <fracContaminate> in file renderer respectively detail the probability that contamination will occur and the proportion of prohibited material that ends up in non-prohibited material. Table <probMislabel> details the probability that prohibited material will be mislabeled as non-prohibited. Finally, table <probDestination> in the

2439 MBMTransporter file details the flow of material generated by renderers to various types of feed
2440 producers.

2441

2442

2443

2444

Table 3-4
The Flow of Infectivity Through the Rendering Process

Figure 3-7 Flow Reference Number	Label^a	Description
1	To P MBM	Infectivity sent to rendering for prohibited MBM
2	SRM Elimination	Infectivity eliminated from potential use in animal feed or human food if specified risk material ban in place
3	Render Elimination	Infectivity removed through inactivation by rendering
4	Contam. NP MBM	Infectivity from P MBM that contaminates NP MBM in mixed rendering facilities
5	Mislabel P MBM	Infectivity in P MBM mislabeled as NP MBM
6	Out after Render	Infectivity in rendered material not used for livestock feed

2445

2446

2447

2448

2449

2450

Notes:

a Entries in the "Label" column refer to the descriptors used in the output tables in the results Section (see Appendix 3A)

2451

3.1.3.3 Feed Production

2452

2453

2454

2455

2456

2457

2458

2459

FDA feed ban regulations restrict use of prohibited MBM to feed manufacturers that produce only prohibited feed, or to manufacturers that produce both prohibited and non-prohibited feed (mixed producers), so long as they adhere to procedures that minimize the risk of contamination. The base case assumes that at mixed facilities, prohibited feed could contaminate non-prohibited feed. In addition, the base case assumes that prohibited feed can be mislabeled in facilities producing both prohibited and non-prohibited feed. The documentation in Appendix 1 (see parameter file feedProducer) details these assumptions in further detail.

2460

2461

2462

When recycled animal tissue (*i.e.*, blood meal or MBM) is used as a supplement to animal feed, the material can be divided among feed portions consumed by many cattle. The base case assumes that infectivity in the blood meal from a single animal is divided among 89 cattle

2463 (see the documentation in Appendix 1 for the <numCowsReceiving> parameter table in the
 2464 proteinInfector parameter file).

2465

2466 How widely infectivity in recycled protein is distributed is more complicated. If the
 2467 infectivity does not contaminate non-prohibited MBM or non-prohibited feed, then it remains
 2468 contained in a single “packet” (*i.e.*, a collection of material that travels together during
 2469 processing) that can be divided among 89 cattle. However, if contamination occurs during the
 2470 rendering process, then a portion of the infectivity is transferred to the affected non-prohibited
 2471 MBM packet. That non-prohibited packet has the potential to expose an additional 89 cattle.
 2472 Finally, if contamination occurs during feed production, it is assumed that a portion of the
 2473 infectivity is transferred to the affected non-prohibited feed packet. That non-prohibited feed
 2474 packet likewise has the potential to expose an additional 89 cattle. Table 3-5 describes the flow
 2475 of cattle infectivity through the feed production process. The parameter tables in files
 2476 feedProducer and feedTransporter detail these assumptions.

2477

2478

2479

2480

Table 3-5
The Flow of Cattle Infectivity through the Feed Production and Use Processes

Figure 3-7 Flow Reference Number	Label ^a	Description
7	To P Feed	Infectivity in P MBM that goes to production of P livestock feed
8	To NP Feed	Infectivity in NP MBM reaching NP Feed
9	Contam NP Feed	Infectivity from P Feed that contaminate NP Feed in mixed feed mills
10	Mislabel NP Feed	Infectivity in P Feed mislabeled as NP Feed
11	To Blood	Infectivity reaching cattle feed through use of blood meal
12	Out After Feed Prod	Infectivity in livestock feed not used for cattle

2481

2482

2483

2484

2485

2486

Notes:

a Entries in the “Label” column refer to the descriptors used in the output tables in the results Section (see Appendix 3A)

2487 **3.1.3.4 On Farm Feeding**

2488 The practice of administrating correctly labeled (*i.e.*, with the label “DO NOT FEED TO
 2489 RUMINANTS”) prohibited feed to cattle on the farm is referred to as “mis-feeding.” The base
 2490 case assumes that correctly labeled prohibited feed will be administered to cattle with a
 2491 probability of 1.6%. Documentation accompanying the <probFeedOK> parameter table in the
 2492 feeder file (see Appendix 1) explains our derivation of this estimate. Table 3-6. describes the
 2493 flow of cattle infectivity on the farm.

2494

2495

2496

2497

**Table 3-6
 The Flow of Cattle Infectivity on the Farm**

Figure 3-7 Flow Reference Number	Label^a	Description
13	Misfed	Infectivity in materials fed to cattle in non-bovine livestock feed
14	To Cattle	Total infectivity reaching cattle through feed

2498

2499 *Notes*

2500

2501

2502

2503

a Entries in the “Label” column refer to the descriptors used in the output tables in the results Section (see Appendix 3A)

2504 **3.1.4 Potential Human Exposure**

2505 The base case assumes that humans can be exposed to BSE infectivity either by directly
 2506 consuming infected cattle organs, such as brain, spinal cord, eyes, and distal ileum, or by
 2507 consuming contaminated products, including meat or processed meat containing spinal cord or
 2508 DRG, or organs containing CNS emboli, such as liver, heart, or kidneys. Table 3-7 details the
 2509 assumed availability of these tissues (see parameter table <probPassFood> in parameter file
 2510 foodInspector).

2511

Table 3-7
Potential Human Exposure

Organs/tissues	Description/Assumptions
Brain	Brain is considered to be a variety meat and reaches the consumers labeled as such. The base case assumes that 1% of all cattle brains are potentially available for direct human consumption.
Spinal cord	Beef spinal cord is considered to be a variety meat and reaches consumers labeled as such. The base case assumes that 1% of the spinal cord is potentially available for human consumption.
Blood	The base case assumes that 5% of the cattle blood is potentially available for human consumption in meat food products (e.g., sausages, blood pudding) and that the infectivity in blood is limited to the potential contribution from brain and spinal cord emboli. In our sensitivity analysis, we investigate the possibility that BSE disease itself also contributes to the infectivity in blood at a concentration that can be as high as the level of detection.
Distal Ileum	Distal ileum is considered to be a variety meat and reaches the consumers labeled as beef intestines. The base case assumes that 1% of the distal ileums are potentially available for human consumption. In the U.S., distal ileum does not reach consumers as natural sausage casings.
Contaminated Organ Meat	Brain and spinal cord are responsible for infectivity in organ meat when air-injected pneumatic stunning is used (not reflected in the base case). Liver, heart, and kidney are sold as variety meat. The base case assumes that 60% of the liver, 50% of the heart, and 25% of the kidneys are potentially available for human consumption.
Eyes	Bovine eyes are considered a variety meat and reach consumers labeled as beef eyes. The base case assumes that 1% of eyes are recovered and potentially available for human consumption.
Contaminated muscle meat	The base case assumes that spinal cord can contaminate edible meat during the splitting process. It is further assumed that other processes, such as steaming or washing do not reduce this contamination. If this source of contamination were important, this assumption could be investigated further.
AMR	Total infectivity in AMR product is the sum of the contributions from spinal cord and DRG contamination. The amount of spinal cord contaminating AMR product depends on whether the spinal cord is removed, as required by FSIS regulation for plants using AMR, and on whether the carcass is mis-split.

**Table 3-7
Potential Human Exposure**

Organs/tissues	Description/Assumptions
Beef on bone	Total infectivity in beef on bone is the sum of the contributions from spinal cord contained in these cuts of meat and DRG attached to these bones. Spinal cord has the potential to reach consumers if it is not removed from the spinal column and if it remains attached to the backbone as bone-in steak. The base case assumes that about 30% of the backbones from steers and heifers are sold bone-in and that because these cuts do not undergo AMR processing, they retain the spinal cord. Although regulations do not require removal of the spinal cord from the backbones that do not undergo AMR (FSIS Directive 7160.2 1997), many slaughterhouses remove it anyway (Brewer 2000). Note that even if the spinal cord or DRG on beef on bone reaches consumers, this material is not likely to be eaten.
Trigeminal Ganglia	The base case assumes that the trigeminal ganglia (TG) does not contaminate cheek meat because it is located at the base of the cranium. Sensitivity analysis investigates the impact of assuming that TG contaminates cheek meat 1% of the time and that when such contamination occurs, it amounts to 1/1000 of the infectivity in TG.

2512

2513 **3.2 Impact of Alternative Assumptions on Cattle Infected and Human BSE**
2514 **Exposure**

2515 We used sensitivity analysis to identify the most important sources of uncertainty. In
2516 particular, we evaluated the extent to which each assumption or parameter individually influences
2517 model predictions for two cumulative outcomes over a 20-year period – the total number of cattle
2518 that become infected after the introduction of 10 infected animals at the beginning of the period,
2519 and the amount of BSE infectivity (quantified in terms of the number of cattle oral ID₅₀s) in food
2520 available for human consumption over that period. The purpose of the sensitivity analysis is to
2521 identify assumptions that should be regarded as candidates for further refinement.

2522

2523 To conduct the sensitivity analysis, we first ran the base case simulation 5,000 times and
2524 recorded the distribution of outcomes for each of the two outcomes of interest (total additional
2525 cattle infected, and total potential human exposure to BSE infectivity). To evaluate the
2526 contribution of an individual parameter or assumption to the uncertainty of these two outcomes,
2527 we altered each assumption, one at a time, setting all other assumptions to their base case values.
2528 In particular, each assumption was individually set equal to its “worst case” bounding value. The
2529 “worst case” value refers to that bounding value for an assumption expected to result in the

2530 largest predicted risk of BSE spreading. For each alternative value, we again ran the simulation
2531 5,000 times and recorded the distribution of values for the two outcomes described above⁴.

2532

2533 Typically, sensitivity analysis also involves estimation of risk for each parameter's best
2534 case value, as well as for each parameter's worst case value. For this project, we determined that
2535 evaluation of the best case values was not necessary because use of base case assumptions yields
2536 a disease reproductive rate constant for BSE in the U.S. (R_0) substantially less than unity. That is,
2537 the model predicts that the prevalence of BSE decreases over time and eventually reaches zero
2538 with near certainty (see Section 4.1). Using more optimistic assumptions for a parameter would
2539 only result in a prediction that the spread of BSE is even more limited than the base case
2540 suggests. Although such a finding would differ quantitatively from the base case, further analysis
2541 is not important because it would not qualitatively alter our conclusions.

2542

2543 The worst case bounding assumptions for each parameter reflect the judgment of this
2544 report's authors given the available scientific literature. Although these assumed values are not
2545 intended to represent absolute bounds on a parameter's value, we have selected them with the
2546 intention of identifying levels beyond which a parameter's true value is very unlikely to fall. The
2547 difference between the simulation results produced using a parameter's base case assumption and
2548 that parameter's worst case bounding assumption represents the maximum extent to which that
2549 parameter's uncertainty can independently increase the predicted spread of BSE.

2550

2551 Instead of conducting deterministic sensitivity analyses for each parameter (*i.e.*,
2552 comparing the simulation results corresponding to the base case to the simulation results
2553 corresponding to each parameter's bounding case), we could have conducted a probabilistic
2554 sensitivity analysis that would characterize the distribution of results corresponding to the
2555 uncertainty associated with each parameter. However, conducting probabilistic analyses would
2556 require specification of a probability distribution for each uncertain parameter over its range of
2557 plausible values, rather than merely identifying the bounds on this range. It is our judgment that
2558 the available information is inadequate to develop the needed probability distributions. The task
2559 is complicated because many of the parameters are not individual numbers but are instead

⁴ One combination of worst case parameters (see Section 4.2.1) was run 780 times because the number of predicted animals infected was often so large that the simulation ran very slowly. The 780 runs required approximately 250 hours of run time on a 3 GHz Windows-compatible computer. Although the limited number of runs reduced the precision of the results, the results were adequately precise for the purpose of

2560 collections of values. Consider, for example, the three multinomial distribution that specifies the
2561 probability of a mis-split, the use of AMR, and the removal of the spinal cord (see Section
2562 3.1.2.7) during the slaughter process.

2563

2564 In addition to conducting a univariate sensitivity analysis, we also evaluate the
2565 synergistic impact of assigning worst case values to multiple sets of simulation parameters
2566 simultaneously. An alternative approach would be to simultaneously sample values from
2567 distributions for each assumption. However, as noted earlier, development of meaningful
2568 distributions for each assumption is not practical given the information that is available.

2569

2570 Because the BSE simulation model has a large number of parameters and assumptions,
2571 and because evaluating each set of assumptions takes a substantial amount of time (in particular,
2572 one set of 5,000 runs takes around nine hours on a 1.8 GHz Intel Pentium IV Processor), we first
2573 eliminated from consideration those parameters for which such analysis is not necessary. The
2574 remainder of Section 3.2 describes this step in further detail. We identify bounds for those
2575 parameters and assumptions not eliminated from further consideration. Qualitative arguments for
2576 eliminating a parameter from further consideration fall into three categories.

2577

2578 First, if the base case results indicate that a set of factors makes only a minor contribution
2579 to either of the key simulation model outcomes, then modifying assumptions related to those
2580 factors is unlikely to influence the results substantially. For example, assumptions related to
2581 blood meal can be eliminated from further consideration because blood meal represents a very
2582 limited portion of the infectivity to which cattle are exposed. The relative importance of blood as
2583 a contributor to infection can be quantified by comparing the mean number of new cases arising
2584 from this mode transmission (0.006) to the mean total for the number of infected animals
2585 excluding those imported at the beginning of the simulation (4.3) (see Table in Section 1 of
2586 Appendix 3A). Because the simulation was run 5,000 times, an average of 0.006 indicates that
2587 over all 5,000 simulation runs, a total of thirty cattle became infected as a result of exposure to
2588 blood meal. That contribution is roughly 0.1% of the total number of animals infected excluding
2589 imports over all 5,000 simulations (21,500).

2590

determining that this combination of worst case assumptions often results in conditions that cause BSE to spread, rather than to die out.

2591 Second, a parameter can be eliminated from consideration if its range of plausible values
2592 and the extent to which changing its value influences the results suggest that the overall impact
2593 will be minimal. For example, as discussed in Section 3.2.1.1, because changing the assumed
2594 size of the cattle population should have virtually no effect on the simulation results, using the
2595 simulation model to evaluate that impact is not necessary.

2596

2597 Finally, if the relationship between a parameter's value and the simulation results is well-
2598 understood, then it is not necessary to use the simulation model to quantify this relationship. For
2599 example, changing the proportion of cattle brains consumed by humans has virtually no impact
2600 on the number of infected cattle for any plausible (*i.e.*, relatively small) value for this parameter.
2601 Moreover, it is clear that doubling this parameter, for example, will double potential human
2602 exposure to BSE from consumption of brains.

2603

2604 The remainder of Section 3.2 reviews the Harvard model's parameters and assumptions,
2605 following the order in which the parameters were presented in Section 3.1. Section 2 in
2606 Appendix 2 to this report details the parameter file changes made for each of these scenarios.

2607

2608 **3.2.1 Cattle Population Dynamics**

2609 **3.2.1.1 Size of Cattle Population, Birth Rates, Slaughter Rates, and Rates of Death** 2610 **Due to Other Causes**

2611 None of these parameters in this category need to be evaluated quantitatively using the
2612 simulation model. First the values for all of these parameters are based on empirical data and
2613 direct observation. We therefore believe it is unlikely that they are incorrect by even as much as
2614 a factor of two. It is our judgment that in most cases, the error affecting any of these parameters
2615 is substantially less than this amount.

2616

2617 As noted in Section 3.1.1.1, the assumed size of the cattle population size (140 million) is
2618 40% larger than the known value for this parameter (around 100 million). However, this
2619 parameter has virtually no impact on the simulation. In particular, the number of animals that
2620 become infected at each time step in the simulation depends on the number of animals infected at
2621 the preceding time step, along with the magnitude of any assumed exogenous introduction of
2622 BSE infectivity. Neither of these factors depends on the size of the cattle population unless the
2623 number of infected animals becomes an appreciable fraction of the total number of animals. In

2624 particular, a very small assumed population size would appreciably increase the probability that
2625 recycled material contaminated with BSE would be consumed by an animal already infected with
2626 BSE, thus decreasing the simulated rate at which the disease would spread among the cattle
2627 population. Because the total number of infected animals in any of the scenarios tested is always
2628 at least several orders of magnitude less than the size of the cattle population, changing the
2629 assumed cattle population size would have virtually no impact on the simulation results.

2630

2631 **3.2.1.2 Proportion of Animals That Die on Farm That Are Rendered**

2632 The worst case scenario assumes that this proportion is 99%.

2633

2634 **3.2.1.3 Cattle Consumption of Bypass Protein and Blood Meal**

2635 Because the protein and blood meal consumption rates are used to probabilistically
2636 allocate infected material among different type/gender/age cattle groups, the absolute magnitudes
2637 of these values do not matter. In particular, multiplying all the consumption rates by a constant
2638 would not affect the simulation results. However, changing the relative magnitudes of these
2639 consumption rates would influence the extent to which cattle in different age groups are exposed
2640 to contaminated feed and blood meal.

2641

2642 Because blood meal is a minor contributor to the spread of BSE (see introduction to
2643 Section 3.2), the assumed relative consumption rate for blood meal is not important. On the other
2644 hand, protein consumption is important because it accounts for the vast majority of the new BSE
2645 infections in the base case. The base case assumes that the calf daily protein consumption rate is
2646 more than half as great as the corresponding rate for older cattle. Because susceptibility to
2647 infection is greater among young animals than it is among older animals, shifting more of the
2648 consumption to calves would increase the rate at which BSE spreads. However, it is unlikely that
2649 the adult bypass protein consumption rate is substantially smaller than we have assumed relative
2650 to calf bypass protein consumption rate. In particular, adult dairy cows must consume bypass
2651 protein to maintain high milk production rates. Because it is unlikely that young cattle are
2652 consuming a substantially greater proportion of the bypass protein than we have assumed, we
2653 conclude that it is unnecessary to evaluate this issue quantitatively.

2654

2655 **3.2.1.4 BSE Dose Response**

2656 Recall that the dose-response assumptions fall into two categories – the shape of the
2657 dose-response relationship (*e.g.*, linear or threshold), and the relationship between age and
2658 relative susceptibility to the BSE agent (*i.e.*, older animals are far less likely to become infected
2659 than younger animals exposed to BSE to the same degree).

2660

2661 Shape of the dose-response relationship: The base case assumes the dose-response
2662 relationship does not have a threshold. If we had assumed a threshold, the number of additional
2663 BSE cases predicted by the simulation would, if anything, have been smaller. There is no
2664 biologically plausible basis for assuming a super-linear dose response relationship. Hence, the
2665 base case assumption must be regarded as either neutral or conservative. For reasons described in
2666 the introduction to Section 3.2, quantitative evaluation of this assumption is therefore not
2667 necessary.

2668

2669 Relative susceptibility vs. age: The assumption that susceptibility to infection decreases
2670 with age is based on both biological considerations (Section 2.1.3) and statistical modeling of the
2671 UK BSE outbreak (Section 3.1.1.4 and Appendix 1, Section 2.3.4). It is therefore unlikely that
2672 susceptibility is independent of age or that it increases with age. However, it is possible that
2673 susceptibility decreases more slowly with respect to age than is assumed in our base case. For the
2674 purpose of evaluating the impact of this assumption on the model's predictions, our worst case
2675 assumes that susceptibility falls approximately half as fast (40% per year) as we assume in the
2676 base case (85% per year), and that as the animal ages, susceptibility asymptotically approaches
2677 10% of its value at birth (same as in base case).

2678

2679 **3.2.1.5 Maternal Transmission**

2680 Maternal transmission is a relatively unimportant mode of transmission in the base case.
2681 Of the approximately 21,500 animals that became infected (excluding imports) during the 5,000
2682 base case simulation runs, 3,200 (15%) were infected due to maternal transmission. It is therefore
2683 unlikely that other plausible values for the parameters influencing maternal transmission would
2684 result in an important number of infections *via* maternal transmission. We therefore do not
2685 quantitatively evaluate the impact of alternative values for assumptions related to this mode of
2686 transmission.

2687

2688 **3.2.1.6 BSE Incubation Period, and Time Until Death Following Onset of Clinical**
2689 **Signs**

2690 BSE incubation period: The incubation period for BSE (*i.e.*, the time between exposure
2691 and development of clinical signs) is somewhat uncertain because the time at which exposure
2692 leading to infection occurs is not known precisely. On the other hand, typical values for this
2693 parameter are relatively well understood because the data from the UK outbreak have been
2694 extensively analyzed, *e.g.*, (Ferguson 1997b; Donnelly 2000). A shorter incubation period could
2695 increase the predicted rate at which BSE spreads because it would increase the probability that an
2696 animal would reach the later stages of infection, when infectivity loads in the animal climb
2697 sharply, prior to being sent to slaughter. To quantify the potential impact of this assumption's
2698 uncertainty, the worst case assumes that the incubation period distribution is a factor of two less
2699 than the base case (*i.e.*, all percentiles of the distribution equal one-half their base case values).

2700

2701 Time until death following the onset of clinical signs: The duration between the onset of
2702 clinical symptoms and death from BSE is well understood because these two events can be
2703 directly observed. The uncertainty associated with this assumption is therefore unlikely to be
2704 substantial. Moreover, it is unlikely that changing this assumption would substantially affect the
2705 simulation's predictions. Once an animal develops clinical signs, we assume that its infectivity
2706 load remains unchanged (10,000 ID₅₀s in the base case). Decreasing the assumed duration
2707 between the onset of signs and death would tend to increase the predicted rate at which BSE
2708 spreads because fewer of the animals that develop clinical signs would be sent to slaughter prior
2709 to dying from BSE. The base case assumes that 90% of the clinical animals sent to slaughter
2710 would be detected and disposed of in a manner that could not expose any additional animals to
2711 the BSE agent. Among those animals that die on the farm (for whatever reason) prior to being
2712 sent to slaughter, the base case assumes that only 15% are disposed of in a manner that cannot
2713 lead to the exposure of any additional animals to BSE. For the purpose of evaluating the
2714 sensitivity of the simulation results to the assumed duration between the development of clinical
2715 BSE signs and death, we assume that for the worst case, this duration is uniformly distributed
2716 between 1 and 4 months.

2717

2718 **3.2.2 The Slaughter Process**2719 **3.2.2.1 Level of Infectivity and Distribution of Infectivity Throughout the Carcass**

2720 Total infectivity in carcass: Because the assumption that 0.1 g of brain from a clinically
2721 affected animal amounts to one ID₅₀ is thought to be conservative (Section 4.2 in (DNV (Det
2722 Norske Veritas) 1997)), it is unlikely that the amount of infectivity in a single animal
2723 substantially exceeds our base case estimate of 10,000 ID₅₀s. In fact, the latest pathogenesis
2724 results indicate that 0.67 g of tissue from a full blown BSE case represents one ID₅₀ (confidence
2725 interval of 0.24g to 1.83 g) (p. 83 in (Vossen 2003)). To address the possibility that continuing
2726 experiments will find that smaller amounts of CNS tissue from clinically affected animals can
2727 result in the transmission of BSE, our worst case assumes that the total infectivity in a clinically
2728 affected animal is as much as 20,000 ID₅₀s.

2729

2730 Distribution of infectivity throughout the carcass: We consider two deviations from the
2731 base case. First, because some experiments have shown that other TSEs can be present in blood
2732 (European Union Scientific Steering Committee 2000e), we consider the possibility that 0.016%
2733 of the infectivity in an animal with BSE is carried in blood. This level of infectivity is consistent
2734 with the assumption that its concentration is at the level of detection in an animal with a full-
2735 blown case of BSE. Our assumptions reflect the judgment of the SSC that one kg of any cattle
2736 tissue negative for infectivity in the mouse bioassay could contain as much as ten oral cattle ID₅₀s
2737 (Annex 2 in (European Union Scientific Steering Committee 2000a)). Hence, we assume that the
2738 3.8 kg of blood dried blood that can be recovered from an average steer (Romans 1974) could
2739 contain 38 cattle oral ID₅₀s.

2740

2741 Second, we consider the possibility that the amount of infectivity in trigeminal ganglia is
2742 higher than the level assumed in the base case. The base case assumes that the trigeminal ganglia
2743 harbor no infectivity until the animal reaches the halfway point between exposure to BSE and
2744 manifestation of clinical signs, after which time, we assume the trigeminal ganglia harbor 2.6% of
2745 the total infectivity. The base case further assumes that no trigeminal ganglia tissue is recovered
2746 for human consumption. The sensitivity analysis evaluates the impact of assuming that 0.1% of
2747 the infectivity in the trigeminal ganglia (as much as 0.0026% of the total infectivity) is recovered
2748 for potential human consumption with 1% probability, and that with 99% probability, none of this
2749 infectivity is recovered for human consumption.

2750

2751 **3.2.2.2 Antemortem Inspection**

2752 The worst case scenario assumes that cattle with clinical signs of BSE will be detected at
2753 antemortem inspection with 50% probability (compared to 90% probability for the base case).

2754

2755 **3.2.2.3 Stunning**

2756 The prevalence of pneumatic stunning devices appears to be zero in the U.S. Even in the
2757 late 1980s, before use of this technology fell out of favor, the proportion of animals stunned using
2758 pneumatic devices was only 15% (see Section 3.1.2.3). For the purpose of evaluating this
2759 assumption's impact on the simulation results, the worst case scenario assumes that the current
2760 prevalence also is 15%.

2761

2762 Both the malfunction probability and the production of emboli have been measured
2763 empirically and are unlikely to be substantially greater than assumed by the base case scenario.
2764 Because the worst case scenario assumption for the prevalence of pneumatic stunners is so
2765 conservative, and because device malfunction and emboli production have been empirically
2766 measured, it is not necessary to consider more conservative assumptions for these last two
2767 parameters.

2768

2769 **3.2.2.4 Exsanguination**

2770 The use of the pneumatic stunner increases the probability that blood gathered by
2771 exsanguinations will be contaminated with brain tissue from zero to 30%. As noted in Section
2772 3.2.2.3, the worst case scenario assumption for the prevalence of pneumatic stunners is very
2773 conservative. The worst case scenario for exsanguinations assumes the same elevated prevalence
2774 for pneumatic stunners of 15%. It also assumes that blood gathered under these circumstances
2775 will be contaminated with 100% probability.

2776

2777 **3.2.2.5 Disposition of Tissues and Potential for Human Exposure**

2778 Table 3-8 details the base case and worst case assumptions regarding the proportion of
2779 tissue recovered for human consumption. Note that none of these sets of assumptions reflect a
2780 specified risk material (SRM) ban.

2781

Table 3-8
Base Case and Worst Case Values for the Proportion of Tissues Recovered from
Cattle for Human Consumption

Tissue	Base Case	Worst Case
AMR Meat	0.98	0.98
Blood	0.05	0.3
Bone (in-bone cuts of meat)	0.98	0.98
Brain	0.01	0.02
Dorsal root ganglia	0	0
Eyes	0.001	0.002
Ileum	0.01	0.02
Heart	0.5	0.6
Kidney	0.25	0.35
Liver	0.6	0.7
Lung	0	0
Muscle	0.98	0.98
Spinal Cord	0.01	0.02
Trigeminal ganglia	0	0

2782

2783

3.2.2.6 Splitting and Aerosolization

2784

2785

2786

2787

2788

2789

2790

2791

2792

2793

3.2.2.7 Disposition of the Spinal Cord and Dorsal Route Ganglia

2794

2795

2796

2797

2798

2799

2800

The base case results indicate that aerosolization is responsible for less than 1% of potential human exposure. Moreover, the aerosolization assumptions, which are based on empirical measurements (see Section 3.1.2.6) are probably conservative because we assume steam washing of the carcass has no effect on the amount of deposited contamination. Because the contribution of aerosolization to potential human exposure appears limited even with these conservative assumptions (contaminated muscle meat in the base case accounts for 0.099 ID_{50S} on average, compared to a total of 39 ID_{50S} available for potential human consumption), it is unnecessary to analyze its contribution to uncertainty quantitatively.

The base case results indicate that contamination of AMR meat accounts for more than half of all potential human exposure to BSE. Because of its apparent importance, we use quantitative sensitivity analysis to evaluate the impact of uncertainty for this set of parameters on the simulation model's predictions.

The assumed proportion of animals processed using AMR is already relatively high for older animals (65% for animals 12 to 23 months, and 60% for animals 24 months or older). Our

2801 worst case scenario reduces the proportion of animals whose spinal cords are removed from 50%
2802 to 10% when AMR is not used, and from 98% to 80% when AMR is used. Finally, the worst
2803 case scenario doubles the assumed base case mis-split frequency from 5% to 10% for animals
2804 below the age of 24 months, and from 8% to 16% among animals 24 months or older.

2805

2806 **3.2.2.8 Postmortem Inspection**

2807 The base case results indicate that almost all human exposure is due to consumption of
2808 AMR (51%), brain (24%), beef on bone (12%), and spinal cord (9%). The contamination in
2809 AMR meat derives from both spinal cord and DRG. The proportion of these tissues passing post
2810 mortem inspection is already very high (90% for brain, spinal cord, and DRG, and 98% for beef
2811 on bone). Hence, increasing the assumed proportion of tissue passing post mortem inspection
2812 would have at most a limited effect on predicted human exposure.

2813

2814 **3.2.2.9 Recovery of Material for Potential Human Consumption**

2815 For material passing post mortem inspection, almost all AMR meat and all beef on bone
2816 are recovered for potential human consumption (98% in both cases). Although the base case
2817 scenario assumes that only 1% of all brains and spinal cords are recovered for human
2818 consumption, it is unlikely that consumption is substantially higher than we have assumed for
2819 either of these tissues. In any case, it is unnecessary to use the simulation model to quantify the
2820 impact of alternative assumptions for the food use recovery parameters because the impact on
2821 human exposure would be linear (*e.g.*, doubling the proportion of brains recovered for human
2822 consumption would double potential human exposure attributable to brain consumption from the
2823 base case value of 9.2 ID_{50S} to 18.4 ID_{50S}).

2824

2825 Nor would any plausible change in the proportion of tissue recovered for potential human
2826 consumption substantially affect the predicted spread of BSE among cattle. Any material
2827 diverted away from potential human consumption would be rendered. The base case predicts that
2828 rendering eliminates 37,000 ID_{50S}, which means that the total amount of infectivity sent to
2829 rendering must exceed 37,000 ID_{50S}. The total amount of infectivity in material recovered for
2830 potential human consumption is approximately 0.1% of this total, so diverting this material to
2831 rendering would have virtually no effect on the predicted spread of BSE.

2832

2833 **3.2.3 Rendering and Feed Production**

2834 For assumptions related to the rendering process, the feed production process, and to on-
 2835 farm feed practices that have been evaluated as part of the uncertainty analysis, Table 3-9 details
 2836 base case and worst case values.
 2837

Table 3-9
Base Case and Worst Case Values for Render Process, Feed Production Process,
and On-Farm Feed Practice Assumptions

Assumption	Base Case	Worst Case
Proportion of animals rendered using various technologies		
Batch (3.1 logs reduction)	5%	5%
Continuous/fat added (2.0 log reductions)	45%	20%
Continuous/no fat added (1.0 log reduction)	45%	70%
Vacuum (no reduction)	5%	5%
Rendering – Contamination of non prohibited MBM by prohibited MBM in mixed facilities		
Probability for a particular prohibited packet	14%	25%
Magnitude of contamination ^a	0.1%	1.0%
Rendering – Probability that prohibited MBM will be mislabeled as non-prohibited MBM when produced by either a mixed or prohibited rendering plant	5%	10%
Feed Production – Contamination of non prohibited MBM by prohibited MBM in mixed facilities		
Probability for a particular prohibited packet	16%	16%
Magnitude of contamination ^a	0.1%	1.0%
Feed Production – Probability that prohibited feed will be mislabeled as non-prohibited feed when produced by either a mixed feed production plant	5%	33%
Probability that correctly labeled prohibited feed will be incorrectly administered to cattle	1.6%	15%

2838

2839 *Notes:*

2840

2841

2842

2843

a. *Refers to the proportion of the prohibited packet that ends up in the non-prohibited packet when contamination occurs.*

2844 **3.2.4 Potential Human Exposure**

2845 Section 3.2.1.9 discusses the worst case assumptions for this set of parameters.

2846

2847 **3.2.5 Simultaneous Evaluation of Multiple Worst Case Assumptions**

2848 As described in the introduction to Section 3.2, we report results for simulations that
 2849 simultaneously assign worst case values to multiple parameters. The sets considered
 2850 simultaneously are the cattle population dynamic assumptions (base case values described in
 2851 Section 3.1.1), the slaughter process assumptions (base case values described in Section 3.1.2),
 2852 and the MBM production, feed production, and feed practice assumptions (base case values
 2853 described in Section 3.1.3). We also evaluate the impact of simultaneously assigning all
 2854 assumptions to their worst case in each possible pair of these sets (cattle population dynamics and
 2855 slaughter process; cattle population dynamics and MBM production, feed production, and feed
 2856 practices; and slaughter process and MBM production, feed production, and feed practices).

2857

2858 **3.2.6 Summary**

2859 Table 3-10 summarizes the worst-case simulations conducted and identifies reasons for
 2860 using the simulation model to quantify the impact of other worst case assumptions.

2861

Table 3-10 Summary of Worst Case Analyses					
Section	Description	Worst Case Simulated	Worst Case Not Simulated Because		
			Base Case Contribution Small	Parameter's Uncertainty and/or Impact on Output Small	Relationship Between Parameter and Simulation Output Well Understood
Cattle Population Dynamics					
3.2.1.1	Cattle population parameters			X	
3.2.1.2	Die on farm render rate	X			
3.2.1.3a	Bypass protein consumption			X	
3.2.1.3b	blood consumption		X		
3.2.1.4a	BSE dose response shape			X	

**Table 3-10
Summary of Worst Case Analyses**

Section	Description	Worst Case Simulated	Worst Case Not Simulated Because		
			Base Case Contribution Small	Parameter's Uncertainty and/or Impact on Output Small	Relationship Between Parameter and Simulation Output Well Understood
3.2.1.4b	BSE susceptibility	X			
3.2.1.5	Maternal transmission		X		
3.2.1.6	BSE incubation and time until death	X			
Slaughter Process					
3.2.2.1a	Total infectivity in carcass	X			
3.2.2.1b	BSE in blood	X			
3.2.2.1c	BSE in trigeminal ganglia	X			
3.2.2.2	Antemortem inspection	X			
3.2.2.3a	Prevalence of pneumatic stunners	X			
3.2.2.3b	Stunner malfunction rate			X	
3.2.2.3c	Emboli formation rate			X	
3.2.2.4	Exsanguination	X			
3.2.2.5	Disposition of tissues for human consumption	X			
3.2.2.6	Splitting		X		
3.2.2.7	Spinal cord and DRG disposition	X			

**Table 3-10
Summary of Worst Case Analyses**

Section	Description	Worst Case Simulated	Worst Case Not Simulated Because		
			Base Case Contribution Small	Parameter's Uncertainty and/or Impact on Output Small	Relationship Between Parameter and Simulation Output Well Understood
3.2.2.8	Postmortem inspection			X	
3.2.2.9	Recovery of material for human consumption			X	X
MBM Production, Feed Production, and Feeding Practices					
3.2.3.1	Render technology	X			
3.2.3.2	MBM contamination	X			
3.2.3.3	MBM mislabeling	X			
3.2.3.4	Feed contamination	X			
3.2.3.5	Feed mislabeling	X			
3.2.3.6	Misfeeding	X			

2862

2863 **3.3 The Base Case: Impact of Alternative Sources of Infectivity**

2864 This section describes how we evaluated the impact of different sources of infectivity on
 2865 the model's predictions. For each of the scenarios considered, we adopted the base case
 2866 assumptions. Infectivity sources evaluated include: spontaneous development of disease (Section
 2867 3.3.1), import of infected cattle or contaminated feed (Section 3.3.2), scrapie in sheep (Section
 2868 3.3.3), chronic wasting disease (CWD) in deer/elk-derived protein supplements (Section 3.3.4),
 2869 CWD from direct contact with infected mule deer, white tail deer and/or elk (Section 3.3.5),
 2870 transmissible mink encephalopathy in mink (Section 3.3.6), a TSE in pigs (Section 3.3.7), a TSE
 2871 in chickens (Section 3.3.8), and recycled waste (Section 3.3.9). Section 3 in Appendix 2 to this
 2872 report details the parameter file changes made for each of these scenarios.

2873

2874 **3.3.1 Spontaneous BSE**

2875 Because there are no measurements of an incidence rate for spontaneous BSE in cattle,
2876 we use the observed age-specific sporadic rate for CJD in humans as a proxy, adjusting the ages
2877 to reflect the difference between the natural lifespan for bovines (approximately 20 years)
2878 (Nowak 1983) and the much longer natural lifespan for humans (approximately 75 years). For
2879 example, the CJD incidence rate for 75-year old humans is assumed to represent the BSE
2880 incidence rate for 20-year old bovines. Making this adjustment and taking into account the
2881 incubation period for BSE yields the age-specific rates that appear in Table 3-11.

2882

2883 Developing age-specific rates is necessary because the often-quoted incidence rate for
2884 sporadic CJD in humans of one per million per year hides substantial variation across age groups.
2885 The disease is virtually never seen before age 30 and has a peak incidence between ages 60 and
2886 65 (Collinge 1997). If this pattern (Figure 3-8) is applicable to sporadic BSE, then estimated
2887 rates in cattle must reflect the age structure of the disease.

2888

2889 Finally, recall that the human CJD rates used to estimate the incidence rate for BSE
2890 represent the rate at which clinical cases appear in the population. Therefore, the rates in Figure
2891 3-8 cannot be used to estimate the rate at which new pre-clinical cases might develop. Instead,
2892 the case age-specific clinical incidence rates must be advanced by the duration of the period
2893 between infection and the manifestation of clinical signs. The median incubation period for BSE
2894 is approximately four years (Section 3.1.1.6). Table 3-11 lists the sporadic BSE rates inferred
2895 from the human sporadic CJD rates. Note that the fourth column from the left (the spontaneous
2896 BSE new infection rate) is similar to the third column from the left (the spontaneous CJD new
2897 clinical case rate) but is offset by three rows, representing four years.

2898

2899
2900
2901
2902

Table 3-11
Human Age Categories, Equivalent Cattle Age Categories, and Age-Specific Human Sporadic CJD Rates^a

Human Age Category (years)	Equivalent Cattle Age Category (years)	Annual Clinical CJD Incidence Rate (per million)	Annual Pre-Clinical BSE Incidence Rate (per million)
0 to 4	0.0 to 1.0	<0.01	0 ^b
5 to 9	1.3 to 2.4	0	< 0.01
10 to 14	2.6 to 3.7	0	<0.01
15 to 19	4.0 to 5.0	0	0.04
20 to 24	5.3 to 6.4	<0.01	0.08
25 to 29	6.6 to 7.7	<0.01	0.16
30 to 34	8.0 to 9.07	0.04	0.45
35 to 39	9.3 to 10.4	0.08	0.99
40 to 44	10.6 to 11.7	0.16	2.14
45 to 49	12.0 to 13.0	0.45	3.55
50 to 54	13.3 to 14.4	0.99	5.03
55 to 59	14.6 to 15.7	2.14	5.75
60 to 64	16.0 to 17.0	3.55	5.6
65 to 69	17.3 to 18.4	5.03	3.94
70 to 74	18.6 to 19.7	5.75	2.42
75 to 79	20.0 to 21.0	5.6	2.42 ^c
80 to 84	21.3 to 22.4	3.94	2.42 ^c
85 +	22.6 +	2.42	2.42 ^c

2903
2904
2905
2906
2907
2908
2909
2910
2911
2912
2913*Notes*

- a* Adapted from (Holman 1995; anonymous 1996)
- b* We assume that the spontaneous CJD case observed in a young child was spongiform degeneration of infancy erroneously coded as CJD
- c* We assume that the spontaneous rate for BSE remains unchanged at ages beyond what can be inferred from the corresponding spontaneous-CJD data

2914

3.3.2 Import of Infected Cattle or Contaminated Cattle Feed

2915

2916

2917

2918

2919

2920

2921

2922

Because APHIS has banned the import of cattle and feed from countries in which the presence of native BSE has been documented (see Section 2.3.2), the import of even a single infected animal is not highly likely. Given that even in the UK, the prevalence of BSE is relatively small, it is implausible that a large number of animals infected with BSE might be imported into the United States.

Nonetheless, in order to evaluate the robustness of the U.S. cattle population against the introduction of BSE-infected animals, we have simulated the introduction of 1, 5, 20, 50, 200,

2923 and 500 infected animals into the U.S. We assume that the imported animals are 12-month old
2924 female dairy cattle that have just become infected. The number of animals was chosen arbitrarily
2925 to bound any potential introduction. Dairy cows were modeled to increase the likelihood that
2926 animals would survive long enough to potentially introduce significant infectivity into the U.S.
2927 system.

2928

2929 In order to evaluate the robustness of the U.S. cattle population against the introduction
2930 of contaminated feed, we have simulated the introduction of feed containing 10,000 ID₅₀s.

2931 Because rendering reduces the amount of infectivity by an average of a factor of approximately
2932 ten, this scenario is equivalent to the import of feed contaminated with the remains of ten full
2933 blown cases of BSE. We also assume that this feed is very widely distributed so that no single
2934 animal receives more 0.2 ID₅₀s. As a result, this scenario does not “waste” any of the infective
2935 agent by sending more to any single animal than is needed to guarantee that animal’s infection.

2936

2937 3.3.3 Domestic Scrapie

2938 The transmission of scrapie from sheep to cattle is one of the primary hypotheses for the
2939 origin of BSE (Horn 2001). Moreover, scrapie is present in the United States. Although no
2940 North American strain of scrapie has been successfully transmitted to cattle exposed orally to the
2941 agent (Cutlip 2001), we evaluate the impact of assuming that such transmission is possible. In
2942 particular, if transmission is possible, we estimate that the rendering of scrapie-infected sheep
2943 could expose the U.S. cattle population to one cattle oral ID₅₀ in feed each month. The derivation
2944 of this estimate is based on the assumption that the number of cattle oral ID₅₀s administered to
2945 cattle is equal to the product of 1) the number of scrapie-infected sheep rendered each year, 2) the
2946 number of sheep oral ID₅₀s per infected animal, 3) the inverse of the cattle-sheep species barrier,
2947 and 4) the proportion of infectivity sent to rendering that survives rendering and is ultimately
2948 administered to cattle.

2949

2950 *Number of scrapie-infected sheep rendered:* We estimate the number of clinical sheep
2951 and the number of pre-clinical sheep separately. A total of approximately 180,000 federally
2952 inspected mature sheep are slaughtered each year in the U.S. (U.S. Department of Agriculture
2953 1998). Assuming that the prevalence of scrapie is the same in the U.S. as it is in the UK (11%)
2954 (Simmons 2000), there are approximately 20,000 sheep with scrapie slaughtered each year.
2955 Although sheep with clinical signs would ordinarily be detected at AM inspection and directed to

2956 incineration, we assume that they are rendered. We assume that 1% of the infected sheep fall into
2957 this category, suggesting that approximately 200 sheep with clinical signs are slaughtered each
2958 year. Note that these estimates are likely to be conservative because the true prevalence of
2959 scrapie in the U.S. is probably less than it is in the UK.

2960

2961 *Number of sheep oral ID₅₀s per clinical scrapie case:* For sheep with clinical scrapie, we
2962 assume that this quantity is 10,000, *i.e.*, the same as the number of cattle oral ID₅₀s per clinical
2963 case of BSE. In order to estimate the amount of infectivity in sheep that are not yet showing
2964 clinical signs of disease, we assume that the infectivity load for scrapie follows the same temporal
2965 pattern as BSE does in cattle (see Figure 3-6). As a result, we estimate the average number of
2966 ID₅₀s in a sheep to equal the time-averaged ID₅₀ burden in cattle over the period prior to the
2967 development of clinical signs. This average is approximately 600 ID₅₀s.

2968

2969 *The cattle-sheep species barrier:* We assume that the species barrier between sheep and
2970 cattle is 1,000, *i.e.*, 1 sheep oral ID₅₀ is equivalent to 0.001 cattle oral ID₅₀s. This assumption is
2971 based on an evaluation of the relative transmissibility of BSE from cattle to mice (Bradley 1999)
2972 and on results from *in vitro* conversion studies (Raymond 1997). The true species barrier is
2973 unknown and may be substantially higher. For example, no North American strain of scrapie has
2974 been successfully transmitted to cattle exposed orally to the agent (Cutlip 2001).

2975

2976 *Proportion of infectivity surviving rendering and administered to cattle:* We used the
2977 simulation model, along with the base case assumptions to estimate the proportion of infectivity
2978 in prohibited material that is ultimately administered to cattle. In particular, we repeatedly
2979 simulated the rendering of a bovine with 1 ID₅₀ using the base case assumptions. Based on 1,000
2980 runs of this simulation, we estimate that under the conditions described the base case, the average
2981 number of ID₅₀s administered to cattle amounted to 8×10^{-4} , *i.e.*, a little less than 0.1% of the
2982 infectivity in prohibited material survives rendering and is ultimately administered to cattle.

2983

2984 *Total infectivity to cattle:* For sheep with clinical scrapie, the product of the four
2985 quantities just described is approximately 2 cattle oral ID₅₀s per year. For sheep not yet showing
2986 clinical signs of disease, the product is approximately 10 cattle oral ID₅₀s per year. The total
2987 amounts to 12 cattle oral ID₅₀s annually, or 1 cattle oral ID₅₀ per month. Note that this estimate
2988 probably overstates actual cattle exposure for two reasons. First, it is likely that the true species

2989 barrier is greater than the value of 1,000 used here. Second, the prevalence of scrapie in the U.S.
2990 is probably less than the UK prevalence rates adopted here.

2991

2992 **3.3.4 Chronic Wasting Disease: Oral Exposure**

2993 The FDA feed ban prohibits the use of rendered material derived from cervids in the
2994 production of feed to be administered to cattle. However, because the ban is not completely
2995 effective, cattle may be exposed to cervid-derived protein and hence to CWD. This section
2996 describes our estimate of an upper bound on this exposure. Annual cattle exposure to CWD
2997 attributable to consumption of cervid-derived protein is the product of the 1) number of diseased
2998 animals harvested, 2) the number of cervid ID₅₀s per slaughtered case, 3) the fraction of animals
2999 rendered, 4) the inverse of the species barrier, and 5) the proportion of infectivity surviving
3000 rendering and administered to cattle. As described below, we estimate that present-day exposures
3001 to CWD among the U.S. cattle population could be as high as two cattle oral ID₅₀s per year,
3002 although the true value is likely to be substantially lower and could be zero.

3003

3004 *Number of diseased animals harvested:* Table 3-12 details the disease prevalence rate,
3005 population size, and annual harvest rate for the three species suspected of harboring CWD. In
3006 one respect, these estimates are likely to overstate the true values because they assume the
3007 prevalence rate for the endemic area applies to the entire population. On the other hand, because
3008 monitoring of CWD is limited to post mortem evaluation of brain tissue, it is possible that
3009 surveillance fails to detect animals with less advanced disease.

3010