Risk of Exposure to BSE Infectivity in UK Sheep

for

Food Standards Agency

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For the

Food Standards Agency

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Management Summary

This Interim Report presents initial results from one of two risk assessment studies commissioned by the Food Standards Agency as part of the contingency planning in the event that a BSE infection is found in sheep in the UK. This study has attempted to quantify the risk of exposure to the human population from BSE infectivity in lamb and sheep meat based on a set of assumed infectivity scenarios. The second study from the Imperial College Department of Infectious Disease Epidemiology has a broader scope of work.

The main steps in the assessment have been:

- To identify the numbers of sheep and lambs slaughtered and consumed in the UK.
- To consider the uses of sheep meat and the quantities of any tissue that may contain infectivity entering the human food chain.
- To assess the potential infectivity in a sheep with BSE and the way the infectivity would develop through the incubation period for the various tissues of interest.
- To develop a simple model that sums the infectivity consumed for each age group and tissue type, combining the infectivity, the amount of each tissue consumed, the relative infectivity, the age factor for each age group and any reduction factor.

About 16 million lambs and sheep were slaughtered in 2000 of which about 13 million would have been consumed in the UK the remainder being exported. There is only limited data on the age of sheep at slaughter, and four age groups have been defined; lambs less than 6 months at slaughter (50%), lambs 6 months to 1 year at slaughter (33%), hoggets (1 to 2 years old) (0.1%) and cull ewes (16%).

It is not known whether or not BSE infectivity is currently present in the UK sheep flock and if it were what the incidence might be. A programme to look for evidence of BSE in sheep diagnosed with scrapie has so far found no cases. However, the experiment is still ongoing and relatively few brains have been tested (about 180). This result does not exclude the possibility of a low level of BSE in sheep. With this uncertainty, the risk assessment is based on the premise that BSE is present in the UK flock using a set of four infectivity scenarios, defined in terms of the percentage of scrapie cases that are BSE; Low (0.01%), Medium (0.1%), High (1%) and Maximum (10%). The prevalence of scrapie in the UK breeding flock is assumed to be about 0.1%.

There are a number of ongoing experimental studies on BSE in sheep. These have shown that the time course and pattern of infection are different to those for BSE in cattle and more in line with scrapie. An important factor is that infectivity is found early in the incubation period in certain tissues, in particular the lymph nodes. Lymph nodes are widely distributed throughout a lamb carcase. This suggests that, if a BSE infection is present in sheep, then there could be infectivity present in lambs at less than 1 year old.

For this assessment it has been assumed that:

1. The infectivity of CNS tissue in a sheep with BSE as an oral dose to humans will be the same as the infectivity of the CNS tissue of a cow with BSE.
2. The relative infectivities of different tissues in a sheep with BSE will be similar to those for scrapie as reported by Hadlow (1982).

Exposure Estimates

The exposure estimates reported here are intended to give an indication of the scale of the risk potential for an assumed prevalence of BSE in sheep. There is significant uncertainty in the estimates and they should not be regarded as absolute measures of risk. They can be used for assessing the benefit of possible risk reduction measures and some are reported below.

The overall exposure of the UK population to any BSE infectivity present in sheep has been estimated to be 3.5 human oral ID_{50} units per year for the Medium infectivity scenario (0.1% scrapie cases as BSE) with a 95 percentile range from 0.02 to 650. The results for the other scenarios are simply a factor of 10 up or down. This is the total infectivity consumed by the whole UK population. The exposure to any one individual would therefore be low. However, the risk levels are not so low that they could be judged to be clearly insignificant.

The results show that about 75% (range: 56% - 84%) of the exposure is due to animals older than 1 year (mainly cull ewes) and that more than 80% (range: 71% - 89%) of the exposure is due to the infectivity in lymph nodes.

Risk Reduction Measures

The results for the distribution of the exposure to infectivity suggest four risk reduction measures for consideration:

RRM-1: No animals older than 1 year allowed in food for human consumption.

RRM -2: All lymph nodes removed from carcase as far as possible. It is assumed that 95% of the lymph tissue would be removed

RRM-3: Use of intestines banned a) from animals older than 1 year, and b) from all animals.

RRM-4: All offals (intestine, liver, thymus, stomach) from animals older than 1 year banned.

Individually, both RRM-1 and RRM-2 reduce the risk of exposure to infectivity by about 75%. By combining them the exposure is reduced by over 90%. A similar risk reduction is obtained by banning the use of all offals from animals over 1 year old (RRM-4) rather than banning the complete animals (RRM-1). The greatest risk reduction (97%) is obtained by combing RRM-2 (removal of all lymph nodes), RRM3b (banning use of intestines from animals of all ages) and RRM-4 (banning the use of all offals from animals over 1 year old).

Sensitivity to Infectivity in Lymph Nodes

From the above, it is apparent that one of the key assumptions for this assessment is the rate of development of infectivity in lymph nodes. The base case assumes that at 6 months to one year infectivity is a factor of 10 less than for a clinical case based on Hadlow's 1982 results. Other studies (e.g Jeffrey *et al*, 2001) have reported signs of infection very early in the incubation period and it has been suggested that the level of infectivity could plateau early. A sensitivity case has therefore been defined with infectivity reaching 100% of the clinical level by the 6-12 month old group, and being a factor of 10 less (e.g.10%) for the less than 6 month group.

This case has then been re-evaluated for the medium scenario (0.1% scrapie cases as BSE). The median of the total infectivity consumed increases by a factor of just over two from 3.5 to 8.3 human oral ID_{50} units per year. RRM-1 (No animals older than 1 year allowed in food for human consumption) now reduces the risk by only 34%. RRM-2 (All lymph nodes removed) however, now reduces the risk by 88% to 1 human oral ID_{50} unit, only slightly

greater than the risk for the base case with this risk reduction measure. The combination of RRM-1 and RRM-2 reduce the risk by 93%.

If infectivity grows more rapidly in lymph tissue than assumed for the base case then RRM-1 is less effective, but RRM-2 remains an effective risk reduction measure.

Recommendations

At the present time it is not possible to predict the risk of exposure from BSE in sheep with any certainty. In order to improve our understanding about the potential risk it is recommended that:

1. The present programme to screen sheep for TSEs in general and BSE in particular should be expanded so that there would be confidence that a low incidence of BSE would be identified.

2. Current research studies on the pathogenesis of BSE in sheep should be expanded to include titrations to report the level of infectivity in selected tissues.

3. Additional data are collected on the total quantity and distribution of potentially infective tissue in the carcass (e.g. lymph nodes, major nerves); cuts of meat and the quantities of potentially infective tissue contained therein (e.g. chops, joints, saddle); and consumption trends in relation to age of animal and cuts of meat across different societal groups.

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1. INTRODUCTION

The theoretical risk of BSE in sheep has been recognised for some time. It is known that sheep were fed concentrate that would have included the same MBM that led to the escalation of BSE in the UK cattle population prior to the ruminant feed ban. It is also known that sheep can be infected with BSE experimentally by feeding them BSE infected brain material. However, a programme to look for the presence of BSE in sheep diagnosed with scrapie has so far found no cases of BSE (some 180 sheep have so far been tested). Unfortunately, there is no easy test to distinguish between BSE in sheep and scrapie, and this requires inoculating an extract of the brain material into a panel of mice and then observing the incubation period of the disease and the resulting lesion patterns in the brain. So far, whilst the results of the tests are encouraging, there are not enough results to be sure that BSE is not present in the sheep flock at a low level.

As part of the contingency planning for this eventuality, the Food Standards Agency commissioned a risk assessment from DNV Consulting to assess the exposure of the human population to BSE infectivity in lamb and sheep meat should BSE be found in the national flock. A second study was also commissioned from the Imperial College Department of Infectious Disease Epidemiology with a broader scope of work.

1.1 Study Objectives

The study objectives, as set out in the project proposal, are:

1. To quantify the possible risk of exposure in the human population to BSE infectivity in lamb and sheep meat based on a range of assumed infectivity scenarios.
2. To identify the main routes of any exposure.
3. To assess the risks to the human population from other routes of exposure to infectivity in sheep.

1.2 Interim Report

This Interim Report has been produced in a relatively short time in order to provide input into a decision making process. It deals only with objectives 1 & 2. The original work programme for this study recognised that there would be gaps in knowledge and data and that it would be necessary to make assumptions in order to carry out the assessment. It was proposed that an expert panel / steering group be established to provide input to the study and to act as a sounding board for the study team. Whilst a Project Steering Group has been established it has not been possible for it to meet in the timeframe for this initial report. Although the team has been able to meet with most of the Steering Group members individually, it has not possible able to use this group as a panel to develop expert judgements about some of the main areas of uncertainty as intended.

The report describes the risk assessment model, the various assumptions needed to assess the risk of exposure to BSE infectivity in sheep and initial results for the exposure to infectivity. Risk reduction measures have been proposed and their effect evaluated. Whilst the assumptions have been subjected to some review following the issue of Version 1 of the report, further review is needed before the results are used to inform decisions.

The study is based on overall data for the United Kingdom and assumed levels of BSE in the national flock. It does not attempt to take account of any regional variations e.g., in the incidence of scrapie.

2. THE UK SHEEP FLOCK

2.1 The UK Sheep Flock

In 2000 the June farm census carried out by DEFRA showed a total of 20,447,000 breeding ewes in the United Kingdom plus 20,855,000 lambs under 1 year old and 959,000 other sheep. The latter will include rams and hoggets. The lamb total represents the numbers on the farm in June; a number of lambs will have been slaughtered before June (about 4 million in February to May 2000) and will not be included in any farm survey.

The numbers of breeding ewes in the UK has remained fairly constant over the past 10 years, averaging 20,800,000.

2.2 Sheep Slaughtered for Meat

DEFRA statistics show that 15.96 million clean sheep and lambs were slaughtered in 2000. Most of these will have been lambs less than 1 year old. The MLC estimate that only around 0.1% of clean sheep are aged over 1 year at slaughter. In addition 2.42 million cull sheep, including rams were slaughtered. Of these 5.1 million of the clean sheep and 0.3 million of the cull ewes were exported.

Table 2.1: Sheep Slaughter Data for 2000 (millions)

Year 2000	**Clean Sheep < 1 year**	**Clean Sheep > 1 year**	**Cull sheep > 1year**
Total number slaughtered in UK	15.94	0.016	2.42
Animal equivalent of exports	5.1		0.3
Animals consumed in UK	10.84	0.016	2.12

The slaughter data do not give any information on the age of the lambs at slaughter. The MLC made an estimate of the average likely ages of lambs slaughtered by month. This is shown in Table 2.2 together with the data for monthly slaughterings in 2000. From the information provided by the MLC an estimate of the proportion of lambs slaughtered at less than 6 months was made. Combining these estimates with the slaughter data results in an estimate that 60% of all lamb slaughtered are less than 6 months old.

From these data four age groups have been defined as a basis for the assessment:

	Number slaughtered and consumed in UK
Lambs less than 6 months at slaughter	6,504,000
Lambs 6 months to 1 year at slaughter	4,336,000
Hoggets (1 to 2 years old)	16,000
Cull ewes	2,120,000

Table 2.2: Estimated Age at Slaughter by Month for 2000

Month	Numbers slaughtered for meat in UK Clean sheep < 1 year	Likely age range (months)	Estimated percentage < 6 months
January	1532	7 - 9	0%
February	1082	8 -1 0	0%
March	962	10 - 12	5%
April	1115	10 - 12	15%
May	893	< 6	90%
June	1119	< 6	100%
July	1610	< 6	100%
August	1424	< 6	100%
September	1481	< 6	100%
October	1834	4 - 8	80%
November	1528	5 - 9	60%
December	1377	6 - 8	40%
Total	**15957**		**60%**

2.3 Scrapie Incidence in Great Britain

Scrapie is a TSE which has been present in the sheep population in the UK for at least 250 years, and is present in many countries. Scrapie appears not to present any risk to human health, and there is no relationship between the occurrence of scrapie and the incidence of CJD in humans.

The incidence of scrapie is difficult to assess as farmers are reluctant to report cases for fear of consequent loss of trade and status. It has been a notifiable disease in the UK since January 1993 and legislation for compulsory slaughter with compensation was implemented in July 1998. However, neither of these measures has had a significant impact on the rate of reporting. Reported cases of scrapie from 1993 are given in Table 2.3, taken from the DEFRA website.

Table 2.3: Reported Scrapie Cases in Great Britain 1993 - 2000

1993	1994	1995	1996	1997	1998	1999	2000
328	235	254	460	508	499	597	568

An anonymous postal survey was carried out in 1998 in order to get a better indication of the prevalence of the disease (Hoinville et al, 1999 & 2000). The results of this survey suggest that in 1998 about 13% of cases were reported. If this is assumed to apply generally, then the actual number of scrapie cases in 2000 would be about 4,400. If the average lifespan of a

breeding ewe is 5 years, this suggests a prevalence of about 0.1% in the 20 million breeding ewes.

The incidence of scrapie in Northern Ireland is less than in Great Britain, with only 1 case reported each year from 1997 to 1999 and 6 cases in 2000 out of a breeding ewe population of 1.3 million.

2.4 Exposure to BSE Infectivity in Feed

DNV carried out a study for the Meat and Livestock Commission in 1998/1999 to assess the likely exposure of the UK sheep flock to BSE infectivity from MBM included in sheep rations (DNV, 1998). This report, together with a similar study to assess the exposure of the cattle population (DNV, 1999), was presented to SEAC.

Some of the main findings of these reports are summarised below.

1. It has been estimated that over the 15 years from 1980 to 1995 some 37,500 bovine oral ID_{50} units of BSE infectivity were fed to ewes in the United Kingdom. Over the same period only some 700 bovine oral ID_{50} units of BSE infectivity were fed to lambs. Most of this infectivity would have been consumed up to 1988, when the ban on ruminant derived protein in ruminant feed was introduced. The infectivity consumed increased rapidly up to 1988, with almost half the total being consumed in 1988.

2. The use of MBM in sheep rations increased steadily from about 0.4% of the UK production in 1975 to 1.2% in 1988. Thus even in the peak year of 1988, the proportion of the MBM production fed to sheep was relatively small.

3. In the year with the greatest exposure to infectivity (1988), the infectivity consumed per ewe is estimated to be 1×10^{-3} bovine oral ID_{50} units per ewe.

4. Over the same period it has been estimated that 1.3×10^{6} (95 percentile range: 1.5×10^{4} to 5.1×10^{6}) bovine oral ID50 units were fed to cattle in Great Britain. Most of this infectivity would have been consumed up to 1988, when the ban on MBM in ruminant feed was introduced.

5. The total exposure of cattle to infectivity (1.3×10^{6} bovine oral ID50 units) can be compared to the total exposure estimated for sheep (37,500 bovine oral ID50 units). Thus the total exposure to sheep is estimated to be about 3% of that to cattle.

6. The majority of the total infectivity from 1982 to 1995 was consumed by the dairy herd (72%), followed by calves under 6 month and calves between 6 months and 1 year (together about 21%).

7. In 1988, the year with the greatest level of infectivity in cattle feed, the average exposure to infectivity was estimated to be approximately 0.05 bovine oral ID_{50} units per head. However this was very unevenly distributed. Dairy cattle are estimated to have the highest per capita consumption (0.15 bovine oral ID_{50} units per head), followed by calves under 6 months (0.06 bovine oral ID_{50} units per head) and calves between 6 months and a year (0.03 bovine oral ID_{50} units per head).

The total number of BSE cases to date is some 178,000 (July 2001). If it is assumed that the number of cases is proportional to the exposure to infectivity in feed, and that this same ratio would apply to sheep, then the total number of sheep BSE cases would be estimated to be 5100. However, as noted above, the average dose to sheep is much less than that to cattle (0.001 bovine oral ID_{50} units per ewe compared with 0.15 bovine oral ID_{50} units per cow for dairy herds, some 150 times less) and the susceptibility may also be less. The total number of cases is therefore likely to be much less than the 5100 estimated above, by a factor of at least 10 and probably more like 100.

This suggests that if sheep were infected by BSE from eating contaminated MBM then the total numbers of cases may have been quite small (up to 500 but perhaps only 50 or so), and would probably not have been noticed as an increase in the background level of scrapie.

The study indicated that almost half of the infectivity would have been consumed in the peak year, 1988 before the ruminant feed ban was introduced. If sheep were infected by this feed then about half of the total numbers of cases could have occurred in one year (about 1990/91). If the number of scrapie cases was similar to that estimated for 2000 (i.e. 4,400), then the proportion of scrapie cases that were BSE would have been in the range 0.5% to 5%.

3. PATHOGENESIS OF BSE IN SHEEP

3.1 BSE in Sheep – Current Uncertainties

A number of fundamental questions remain unanswered from current research into BSE in sheep and its potential impact on individual animals and the sheep population as a whole. Some of the major areas of uncertainty are summarised below:

Infective Dose
- Amount of infective material required for transmission under field conditions
- Doses to which animals may be exposed
- Species barriers
  - Cattle : sheep
  - Sheep : human
  - Sheep : sheep (passaged infection)

Transmission
- Routes of infection (e.g. oral, through skin)
- Potential for vertical transmission
- The potential for transmission of infective material at or around the time of birth (e.g. via the placenta)
- Differences in infectivity between ruminant and pre-ruminant phases
- Likelihood of carrier status animals
- Whether doses are likely to be single or repeated
- The role of genotyping in conferring protection

Experimental Limitations
- Lack of rapid screening and diagnostic tests, particularly for subclinical infections
- Detection levels (sensitivity of mouse and immunohistochemical assays)
- Use of large inocula that may not closely represent realistic field exposure levels
- Potential for dilution of positive tissue with that from negative animals in pooled samples (‘false negatives’)
- Prolonged experimental durations
- Relatively small sample sizes
- Resource requirements when sampling a large number of tissues and establishing a time course for infection

These practical difficulties facing researchers have meant that much of the data required for the risk assessment has had to be derived from a number of related sources. As such, a number of assumptions have been made regarding the pathogenesis of BSE in sheep for use in the risk assessment. Available information and assumptions are discussed in detail in the following sections.

3.2 BSE in Sheep – Data Sources

The vast majority of infective material in cattle with BSE is associated with the central nervous system, (CNS), which includes the brain, spinal cord, dorsal root ganglia (DRG), and trigeminal root ganglia (TRG). Infectivity increases over time to reach maximal levels at the time of clinical disease. However, a growing body of evidence from experimental studies of

BSE in sheep indicates that the time course and pattern of infection are very different to those for BSE in cattle, and are indeed more in line with scrapie (Jeffrey *et al*, 2001).

For the purposes of this risk assessment it will be assumed that BSE in sheep follows a pattern of infectivity consistent with that of scrapie. Thus, a combination of data sources will be used representing data from studies of both scrapie and BSE in sheep, to build a model of the tissues affected, time course and titres of infectivity.

3.3 Scrapie in Sheep

Hadlow and co-workers (1979 & 1982) carried out much of the initial transmission work on scrapie in sheep, providing information on both the time course of infection and levels of infectivity in various tissues. They studied the temporal distribution of infectivity in naturally infected Suffolk sheep. This study remains the main source of data on levels of infectivity in tissues other than the CNS in sheep. In order to study preclinical infection, young sheep were selected from high risk families, that is families in which scrapie occurred in parents or progeny, or both, in at least two of the last three generations in the pedigree. The main results for the different ages examined are summarised in Table 3.1, with a summary of the levels of infectivity given in Table 3.2.

Table 3.1: Summary of Infectivity found in Suffolk Sheep

Age	Number examined	Clinical disease?	Tissues Examined	Result	Scrapie history of parents
0 months (at birth)	6	No	Retropharyngeal, prescapular, prefemoral, & mesenteric lymph nodes, thymus, spleen, & ileum	No Infectivity	One dam
3 months	2	No	Retropharyngeal, prescapular, & mesenteric lymph nodes, tonsil, spleen, & ileum	No Infectivity	None
7 - 8 months	8	No	As above	No Infectivity	None of the dams, and 2 sires
10 - 14 months	15	No	Infectivity found in lymphatic tissues and intestine	Infectivity in 8 of 15 See Table 3.2	All infected lambs were progeny of ewes that later became affected with scrapie
25 months	3	No	Infectivity present in ileum, proximal colon and widely distributed in lymphatic tissue. First signs in CNS but at low titre.	Infectivity in 1 of 3	Dam of infected ewe plus one other died of scrapie
34 - 57 months	9	Yes	Infectivity present in range of non-neural and neural tissues.	Infected See Table 3.2	5 were progeny of ewes that died of scrapie

Hadlow's results suggest that there is no detectable infectivity in lambs aged 7 - 8 months. However, none of the dams and only 2 of the sires of these eight lambs came down with scrapie, in contrast to the group of 10-14 month old lambs in which all of the infected animals (8 of a group of 15) were progeny of dams that later were affected with scrapie. Thus, even though all lambs were chosen to be from high risk stock, there is a chance that the group sampled at 7 – 8 months would not have gone on to develop scrapie.

From Table 3.2 the following conclusions for use in this risk assessment can be drawn:

1. The CNS tissues of lambs aged 10 - 14 months had no detectable infectivity; the level of infectivity is therefore at least 3 logs (1000 x) below the infectivity in the clinical animals.
2. The infectivity in lymph nodes, tonsil and spleen of the 10 - 14 age group is about one log (10 x) below the infectivity in the clinical animals.
3. The infectivity in the ileum and proximal colon is only slightly less (less than 1 log) in the 10 - 14 month preclinical group than in the clinical animals.

Van Keulen *et al* (2000) examined the appearance of PrP^{Sc} in sheep naturally infected with scrapie. The conclusions reached were broadly similar to Hadlow's earlier study. Signs of PrP^{Sc} were present in the intestine as early as 5 months post infection, with subsequent spread to the enteric nervous system and spinal cord after 10 months. Samples taken beyond that point showed PrP^{Sc} throughout the alimentary canal and central nervous system, suggesting widespread infection by 21 months.

3.4 Experimentally Induced BSE in Sheep

Studies have established that sheep can be experimentally infected with BSE, and that the resulting condition bears a close resemblance to scrapie (Jeffrey *et al*, 2001). A full critical review of work carried out on BSE in sheep falls outwith the scope of this assessment. However, the following information summarises the main points from studies carried out to date, and seeks to identify common trends in the data.

Foster *et al* (2001) examined the distribution of BSE in sheep using immunohistochemical techniques. Animals were infected orally with 5g equivalent of BSE infected bovine brain material and all sheep used in the study were from genotypes known to be susceptible to scrapie. Samples were collected from animals showing advanced signs of clinical disease, which was observed between 553 to 1073 days post infection.

Strongly staining tissues included brain, spinal cord, tonsil and some lymph nodes. Tissues showing less staining included parts of the intestine, particularly Peyer's patches, with some slight staining in areas of the peripheral nervous system and spleen. The pattern of staining in tissues sampled was broadly similar between animals across the range of time for clinical signs to become apparent (i.e. 553 to 1073 days). As all animals were killed at the onset of clinical disease, no information on the development of the disease and its subsequent spread through tissues over time was available.

Table 3.2: Infectivity Titres of Scrapie in Suffolk Sheep

	Preclinical Infection 10-14 months		**Clinical Infection**	
Tissue	**Titre Mean ± SEM of (n) samples**		**Titre Mean ± SEM of (n) samples**	
Category 1				
Brain	ND		5.6 ± 0.2	(51)
Spinal cord	ND		5.4 ± 0.3	(9)
Category II				
Ileum	4.3 ± 0.4	(4)	4.7 ± 0.1	(9)
Lymph nodes	3.5 ± 0.2	(21)	4.4 ± 0.08	(42)
Proximal colon	4.3 ± 0.4	(4)	4.5 ± 0.2	(9)
Spleen	3.3 ± 0.5	(6)	4.5 ± 0.3	(9)
Tonsil	3.3 ± 0.4	(4)	4.5 ± 0.3	(8)
Category III				
Sciatic nerve	ND		3.3 ± 0.3	(8)
Distal colon	ND		3.0 ± 0.2	(7)
Thymus	ND		2.8 ± 0.6	(2)
Bone marrow	ND		2.1	(1)
Liver	ND		2.4	(1)
Lung	ND		ND	
Pancreas	ND		2.5	(1)
Category IV				
Blood clot	ND		ND	
Heart muscle	ND		ND	
Kidney	ND		ND	
Mammary gland	ND		ND	
Milk	ND		ND	
Serum	ND		ND	
Skeletal muscle	ND		ND	
Testis	ND		ND	

Notes:
1. All results taken from Hadlow (1982).
2. Titres are expressed as arithmetic means of log 10 mouse i/c /g
3. Mean titres calculated not taking account of any ND samples
4. ND = not detectable (> 2.0 log 10 mouse i/c /g)

Jeffrey *et al* (2001) carried out time series experiments in sheep, orally infected with 5g of BSE brain tissue and killed at intervals of between 4 and 22 months, or with the onset of clinical illness. This series of experiments is currently ongoing (MAFF Research Project Number SE1929). Early detection of disease specific PrP was found to occur in the retropharangeal lymph node at 4 months post infection. However, by 16 months PrP^{Sc} was detected in viscera, and the central nervous systems. By 22 months post injection,

widespread accumulation of PrP^{Sc} was evident throughout the lymph system, tonsil, spleen, intestine and stomach. Additional information on this experiment is now available indicating that other tissues including liver have been found to show evidence of infection after 16 months (Bellworthy *et al*, unpublished). It is noted that presence of PrP^{Sc} is thought to equate to infectivity by mouse bioassay but this has not yet been demonstrated.

As part of the same series of experiments, Suffolk sheep have been similarly infected with BSE and results are becoming available (Bellworthy *et al*, unpublished). Although these experiments are ongoing and further samples remain to be assayed, by 10 months post infection tissues including lymph nodes, tonsil, spleen, Peyer's patch, brain and spinal cord have been identified as showing signs of infection.

Although not all animals sampled were found to show consistent signs of infectivity in all tissues, some evidence of a trend does appear to be becoming apparent. Infection tends to be detected early in lymph nodes, followed by spleen, tonsil, tissues of the alimentary tract and CNS.

3.5 Tissue Categorisation and Development of Infectivity with Age

There is currently no definitive literature listing the tissues affected by BSE in sheep, nor their titres of infectivity over time. Despite the fact that the knowledge base is incomplete, the following sections describe what is a growing body of information. Tissues likely to be of primary importance in the event of BSE in sheep are described under the categories listed in the SEAC report (1994). For the purposes of this assessment some redefinition and aggregation of tissues has been attempted in order to provide information at a meaningful level appropriate to tissues that may be of importance to the food chain.

When considering the development of infectivity with age, and especially when comparing the results from different experiments, it is better to consider times as fractions of the incubation period for the experimental animal rather than absolute time (Bram Schreuder, Institute for Animal Science and Health, Lelystad, Netherlands; personal communication). This is because in many cases animals with the shortest incubation periods will have been used in the experiments.

The available data are then used to propose factors to define the relative infectivity for each of the tissues of interest for the four age groups being considered (as defined in Section 2.2). The resulting factors are summarised in Table 3.3, with the rationale for the choice given in the following sections. Each factor represents the percentage of a fully infected animal for that tissue in each age group. In all cases it is assumed that any older sheep in the "cull ewe" group with positive infectivity will have the same infectivity as a clinical case. It is recognised that the factors in Table 3.3 relate to the most susceptible genotypes that will have the shortest incubation periods. This should be conservative, and any animals that were to be infected with BSE are likely to be of a susceptible genotype.

3.5.1 Category I

- Brain and Spinal Cord

Brain and spinal cord are the tissues that will have the highest level of infectivity in a clinical case (SEAC, 1974). Hadlow (1982) showed that infected lambs of 10 to 14 months old had

no detectable infectivity in CNS tissues and that low titres of infectivity were first detected at 25 months. Some research evidence from studies of scrapie and BSE in sheep have shown some indicators of infection with TSEs in brain and spinal cord as early as 10 months post infection (Bellworthy, unpublished data & van Keulen *et al*, 2000). However, it is considered highly probable that infectivity titres at this point will be greatly lower than those present in a clinically affected animal.

Hadlow's data as given in Table 3.2 indicate that the titre in infected preclinical lambs aged 10 to 14 months was at least 3 logs less than in the clinical cases. This is assumed to apply to the 6 month to 1 year age group which is assigned a factor of 0.1% in Table 3.3, with the titre for the less than 6 months group further lowered by a factor of 10.

3.5.2 Category II

- Intestine

A variety of studies have examined different areas of the alimentary canal. For the purposes of this assessment the digestive tract has been subdivided into intestine and stomach (see Category III). Intestine has been taken as a general term for the area of the alimentary canal posterior to the stomach, comprising duodenum, jejunum, ileum, caecum, and colon. Areas of the intestine including duodenum and jejunum are reported to show signs of positivity as early as 5 months for scrapie and 7 months for BSE infected animals (Van Keulen *et al*, 2000 & Bellworthy, unpublished data).

Hadlow's data suggest that the infectivity in some intestinal tissues (proximal colon) was only a factor of 2 or so less in the infected preclinical lambs aged 10 to 14 months, whilst infectivity was not detectable in this group for the distal colon. The 6 month to 1 year age group has been assigned a factor of 50%, and as no infectivity was detected at less than 6 months a factor of 1% is assumed.

- Lymph nodes

Lymph nodes and Peyer's patches appear to be amongst the first tissues affected in the disease process, and have been reported to show signs of infection as early as 4 months post infection (Jeffrey *et al*, 2001). The assumption will therefore be made that lymph nodes are likely to become infected early in the disease process.

Hadlow's data (Table 3.2) suggest that infectivity in lymph nodes was a factor of 10 less in the infected preclinical lambs aged 10 to 14 months than in the clinical cases. A factor of 10% has been assigned to the 6 month to 1 year age group, and 1% to the less than 6 month group.

- Spleen and Tonsil

Spleen and tonsil have both been found to contain signs of infection after 10 months in cases of BSE, and to a similar timescale for scrapie (Jeffrey *et al*, 2001, Hadlow *et al*, 1979). Hadlow's data suggest similar levels of infectivity as for lymph nodes and the same factors have been applied.

3.5.3 Category III

- Stomach

There are no data available for levels of infectivity in stomach components, which is assumed to include oesophagus, rumen, reticulum, omasum and abomasum, although the indications are that infectivity will be less than that in the intestine. Van Keulen *et al* (2000) demonstrated positive material present in the abomasum after 10 months in scrapie infected animals, whereas the earliest reported incidence for BSE was 22 months post infection (Jeffrey *et al*, 2001). The development with age is assumed to be the same as for lymph nodes.

- Liver and Thymus

Liver has been reported as showing signs of positivity at 16 months post infection, whereas thymus has only been reported as positive in clinical cases after 24 months (Bellworthy, unpublished data). Although liver was reported to have low infectivity titres in the Hadlow studies (1982), it is of note that in recent experimental studies infectivity has been observed relatively early in the disease process. The development of infectivity with age is assumed to be the same as for lymph nodes.

3.5.4 Category IV

Little information on infection could be found for heart muscle and kidney. However, these tissues will be assumed to have relatively low titres of infectivity. The development of infectivity with age is again assumed to be the same as for lymph nodes.

Table 3.3: Assumed Development of Infectivity by Age and Tissue

		Relative infectivity by age			
		Lambs < 6 months	Lambs > 6 months	Hoggets 1 - 2 years	Cull ewes
Category 1					
	Brain	.01%	.1%	10.0%	100%
	Spinal Cord	.01%	.1%	10.0%	100%
Category 2					
	Lymph nodes	1.0%	10.0%	50.0%	100%
	Spleen	1.0%	10.0%	50.0%	100%
	Tonsil	1.0%	10.0%	50.0%	100%
	Intestine	1.0%	50.0%	50.0%	100%
Category 3					
	Stomach	1.0%	10.0%	50.0%	100%
	Liver	1.0%	10.0%	50.0%	100%
	Thymus	1.0%	10.0%	50.0%	100%
Category 4					
	Heart	1.0%	10.0%	50.0%	100%
	Kidney	1.0%	10.0%	50.0%	100%

3.5.5 Summary

In summary, a number of studies have now been completed or are in progress, and a body of useful information is becoming available. Unfortunately, information on the titres of infectivity present in tissues over time is still scarce, with much of the work employing qualitative techniques (e.g. immunohistochemistry (IHC)) to identify signs of infection. Work by Hadlow *et al* (1982) on scrapie remains the best available information on the likely titres of infectivity for BSE in sheep, but it must be stressed that much of these data are based on relatively few animals.

The sequence of tissues affected appears to be relatively consistent across studies, although differences do exist. This may be due to a combination of different tissue sampling protocols and diagnostic testing methodologies. However, it might also be an indication that the pattern of infectivity could differ between animals for a number of reasons. These might include age/development stage of animal, route of infection, dose, host genotype, or a combination of these and other factors.

Information summarised in this section has been translated into a somewhat stylised pattern of pathogenesis based upon the best available information at this time. As a consequence, drawing conclusions on the likely sequence of events and titres of infectivity from the available data has required the use of a significant degree of judgement and assumption in arriving at the figures presented.

4. INFECTIVITY

There is little information about the potential infectivity of infected tissues in a sheep with BSE. In order to make some assessment it will be necessary to draw parallels with both scrapie and BSE in cattle. Two main assumptions will be made:

3. The relative infectivities of different tissues in a sheep with BSE will be similar to those for scrapie as reported by Hadlow (1982) and presented in the SEAC (1994) report.
4. The infectivity of CNS tissue in a sheep with BSE as an oral dose to humans will be assumed to be the same as the infectivity of the CNS tissue of a cow with BSE.

The infectivity of the BSE agent has been considered in detail by the Scientific Steering Committee (SSC) of the European Commission and their assessment presented in their opinion adopted at their meeting on the 13-14 April 2000 "Oral Exposure of Humans to the BSE Agent: Infective Dose and Species Barrier". This opinion is used as the basis for this risk assessment.

The infectivity (i.e. the potential to cause infection) of tissue from an animal with BSE is expressed in terms of its Infectious Dose 50 (ID_{50}) value. This is the dose (i.e. the quantity which each person would need to consume) to cause infection of 50% of the exposed population. This term acknowledges that some people may become infected from much smaller doses, while others may be uninfected after consuming much larger doses.

4.1 Infectivity of CNS Tissue in Cattle with BSE

4.1.1 Infectious Dose

The SSC concluded that the various approaches to assessing the infectivity from a clinically infected brain yielded a range of values from 10^1 to 10^3 cattle oral ID_{50}/g. They noted that the higher value may represent a worst case scenario if the oral route is more efficient than data suggests and a particularly high titre of infected brain is sampled. They conclude that such a high dose cannot be ruled out. The lower value is based in part on the results of the attack rate experiment carried out by the UK MAFF. It is noted that this experiment is incomplete and that it is not possible to obtain a final value for the infectious dose. The SSC gives some weight to the calculations of Diringer (1999) using the results of published and peer reviewed experiments. This results in an estimated infectious dose of 50 cattle oral ID_{50}/g.

From this data it is proposed to adopt a distribution of values ranging from 10 to 10^3 cattle oral ID_{50}/g with a best estimate value of 50 cattle oral ID_{50}/g.

4.1.2 Species barrier

The infectivity of BSE for humans is believed to be lower than in cattle due to the species barrier. The species barrier in this context is defined as the factor by which the effective infectivity in one species is reduced when given to a second species. Thus, if the cattle–human species barrier was 100, it would mean that 100 times more infective material would be required to infect a man than a bovine.

In their opinion, the SSC concluded that the size of the species barrier between BSE in ruminants and BSE in humans (vCJD) is not known. They considered that a worst case

scenario considering no (=1) species barrier should be included, although available evidence indicates that values greater than one are likely to be more realistic. They recommended that, until more scientific data are available, for risk assessments of human exposure to potentially BSE infected products, a species barrier of about 1 should be considered as a worst case scenario and that the range from 10^4 to 10^1 be considered. This supports the assumptions made by DNV in previous risk assessments in which the species barrier was represented as a distribution using values of 10, 100, 1000 and 10,000 with equal probabilities, and a 1% probability of it being 1 (DNV, 1997 a & b). It is proposed to use the same distribution in this assessment.

4.2 Assumed Infectivity of BSE Infectivity in Sheep

The infectivity density of CNS tissue from an infected bovine to humans is obtained from the product of the infectious dose for cattle and the cattle human species barrier. Combining the distributions given above in a probabilistic assessment, results in an estimate of the median value of the infectivity density for humans of 0.25 human oral ID_{50} per gram, with a 95 percentile range of 0.002 to 50. This is assumed to apply to the CNS tissue of a BSE infectivity in sheep. Relative infectivities of other tissues are based on the work of Hadlow as presented in Table 3.1 These are summarised in Table 4.1. The infectivity of each tissue to humans is then obtained from the calculated value of the infectivity for CNS tissue multiplied by the relative infectivity for the relevant tissue category.

Table 4.1: Summary of Assumed Infectivity of BSE Infectivity in Sheep

Tissue	Titre Mouse i/c	Relative Infectivity
Category I Brain Spinal Cord	5.5.	1
Category II Lymph nodes Spleen Tonsil	4.5	0.1
Category III Stomach Liver Thymus	2	3.2×10^{-4}
Category IV Heart Kidney	1	3.2×10^{-5}

5. CONSUMPTION OF LAMB AND SHEEP MEAT

5.1 Overall Direction of Sheep Meat

The overall direction of sheep meat in the UK domestic market is summarised in Table 5.1. As indicated in Table 2.1, about 10.8 million lambs were slaughtered for consumption in the UK in 2000. This would represent about 195,000 tonnes of product. About two thirds of this production is sold as primary cuts through retail outlets and about one third through restaurants and catering facilities. Only a negligible amount of UK lamb is used in the processing sector. About ¼ of the retail sales are through butchers with the remainder being through the supermarkets.

In 1999 the MLC carried out a study of the factors affecting the Ewe market in Great Britain. They found that the ethnic market accounts for around 94% of the domestic market for ewe meat, with the majority being Halal slaughtered.

Table 5.1: Direction of Sheep Meat on UK Domestic Market

		Number slaughtered (million)	Weight (tonnes)
Lamb	Retail - primary cuts		
	Butchers	1.8	32,400
	Supermarkets	5.4	97,200
	Food service	3.6	64,800
	Total Lamb	10.8	195,000
Mutton	Ethnic market		
	Primary cuts & processed	2.01	56,300
	Other processed food	0.13	3,600
	Total Mutton	2.14	59,900

Notes:
1. Lamb: all animals aged under 1 year at slaughter; average carcase weight = 18kg.
2. Mutton: all animals aged over 1 year at slaughter; average carcase weight = 28kg.

5.2 SRM Controls

Specified Risk Material (SRM) includes those tissues of cattle, sheep and goats which are known to, or might potentially, harbour detectable BSE infectivity in infected animals. The purpose of the SRM controls is to ensure that such material is excluded from the human and animal feed chains.

SRM controls were originally introduced just for cattle in 1989, but were extended to sheep and goats in 1996 under the Heads of Sheep and Goats Order 1996, which prohibited the sale for human consumption of the heads of sheep or goats. SRM controls have been regularly amended and updated, most recently to bring them into line with EU wide SRM controls. For sheep and goats, SRM comprises:

- Skull including the brains and eyes, tonsils, spinal cord of animals aged 12 months or that have a permanent incisor erupted through the gum, and spleen of all animals.

As heads of all sheep had been defined as SRM in previous UK legislation this has now become normal practice, and heads are still removed and do not normally enter the human food chain. They may now be rendered as clean material as opposed to SRM. However, there is still a small market for lambs brains.

5.3 Sheep Tissues with Potential Infectivity

There is little information available on the consumption and utilisation of sheep offals. The best information is contained in the study carried out by Leatherhead Food RA and the Meat and Livestock Commission for MAFF in 1997 (Audit of Bovine and Ovine Slaughter and By-products Sector). The study covered the 15 year period from 1980 to 1995, and most data are given as averages for this period. Clearly this period pre-dates SRM controls, and this has been taken into account where appropriate in using the data.

This study has concentrated on those tissues that are likely to contain infectivity in an infected animal and in tissues that are used for human consumption. Tissues that are used primarily in pet food or rendering are not included. The data and assumptions made are summarised in Table 5.2. In general the Leatherhead report does not distinguish between lamb and mutton, and so the same values have been used.

Table 5.2: Utilisation of Sheep Offals in Food

Tissue	Weight (kg)	Utilisation in food		Notes
		Lamb	Mutton	
Brain	0.1	5%	0%	Head removed at slaughter - SRM if older than 1 year
Spinal cord & DRG	0.04	20%	0%	See section 5.3.1 - SRM if older than 1 year
Kidney	0.1	100%	100%	
Heart	0.2	50%	50%	
Thymus	0.3	100%	100%	
Liver	0.61	100%	100%	
Stomach (rumen)	1.0	10%	10%	Section 5.3.4
Intestines	1.2	90%	90%	Section 5.3.3
Lymph nodes	0.04	100%	100%	Section 5.3.2

5.3.1 Brain & Spinal Cord

The brain and spinal cord is classed as SRM for any animals older than 1 year and so would not enter the food chain (apart from any possible contamination). For lamb there is no data on the proportion of cuts that would include spinal cord (e.g. saddle of lamb or Barnsley chops that include a cross-section of the vertebral column) or how often a butcher would remove the spinal cord when cutting chops etc. Advice from the Meat and Livestock Commission (David Croston, personal communication) suggests that lamb prepared by supermarket facilities will normally have a guideline that would require removal of the spinal cord. However there is no standard for retail butchers and the MLC estimate that some 40% (range 30 - 50%) of the spinal cord could end up in meat sold to the consumer. It is assumed that this also applies to foodservice facilities. From Table 5.1 it can be seen that butchers and food service account for 50% of lamb consumption. Thus it can be assumed that 20% (15% - 25%) of spinal cords from lambs could be in meat sold to the consumer. For the present it is assumed that all of this is consumed.

Whilst most heads are removed at the abattoir and sent for rendering it is known that there is still a small market for lambs brains. There are no data on the amount of brain sold for consumption. It has been assumed that 5% of lambs brains are consumed; it is thought that this is a high estimate.

5.3.2 Lymph Nodes

It is known that lymph nodes could have infectivity early in the incubation period. They are also well distributed throughout a lamb or sheep carcase and would be difficult to remove. In 1998 the MLC initiated some work to identify any lymph nodes present in a typical dressed carcase (Mike Owen, personal communication). Fifteen groups of lymph nodes were identified in the sheep carcase, and are shown in Figure 5.1. Twenty lamb carcases averaging 18kg were butchered to assess the optimal time for removal, the removal time, the weight of lymph nodes and the success rate of the removal process. It was found that the number and size of nodes varied in each carcase, but that the average weight of lymph nodes from an 18kg carcase is approximately 40 grams of which the two largest, (popliteal and prescapular) make up 40%.

In addition, 40 cull ewe carcases were also studied. This showed that the weight of lymph nodes for cull ewes were related to carcase weight, with weights ranging from 40 grams in a 25 kg carcase to 60 grams in a 55 kg carcase. The average weight of nodes was 49 grams per carcase.

Dissection of the carcases after node removal showed that two thirds had small (0.1 to 0.3 gram) deposits of lymphatic tissue remaining. This indicated that more than 99% of the lymphatic tissue was removed from all carcases.

5.3.3 Intestine

Sheep intestines are used to make natural sausage casings. It is estimated that between 5 and 10% of casings are not recovered or are unusable, and that about 75% of casings are exported.

Processing of sheep intestines for sausage casings: sausage casings are prepared from the small intestine of sheep. The small intestine is separated from the attached organs (stomach, spleen etc) and placed on the pulling table. A natural break occurs near the end of the small intestine allowing consistent separation from the ileum. The remainder of the small intestine (the duodenum to the jejenum) is cleaned and mechanically reduced to leave the submucosa layer only. The casing cleaning equipment consists of conveyor belts, holding (soak) tanks, water sprinklers and rollers through which the casings are transported. A report from a study in which samples of sheep intestine from different stages of the cleaning process were histologically examined by the Faculty of Veterinary Medicine at the University of Utrecht states that "Patches of Peyer were thoroughly removed during the process".

On the basis of the above it is assumed that the casings cleaning process will lead to a substantial reduction in any infectivity present; this is assumed to be a factor of 100.

5.3.4 Stomach

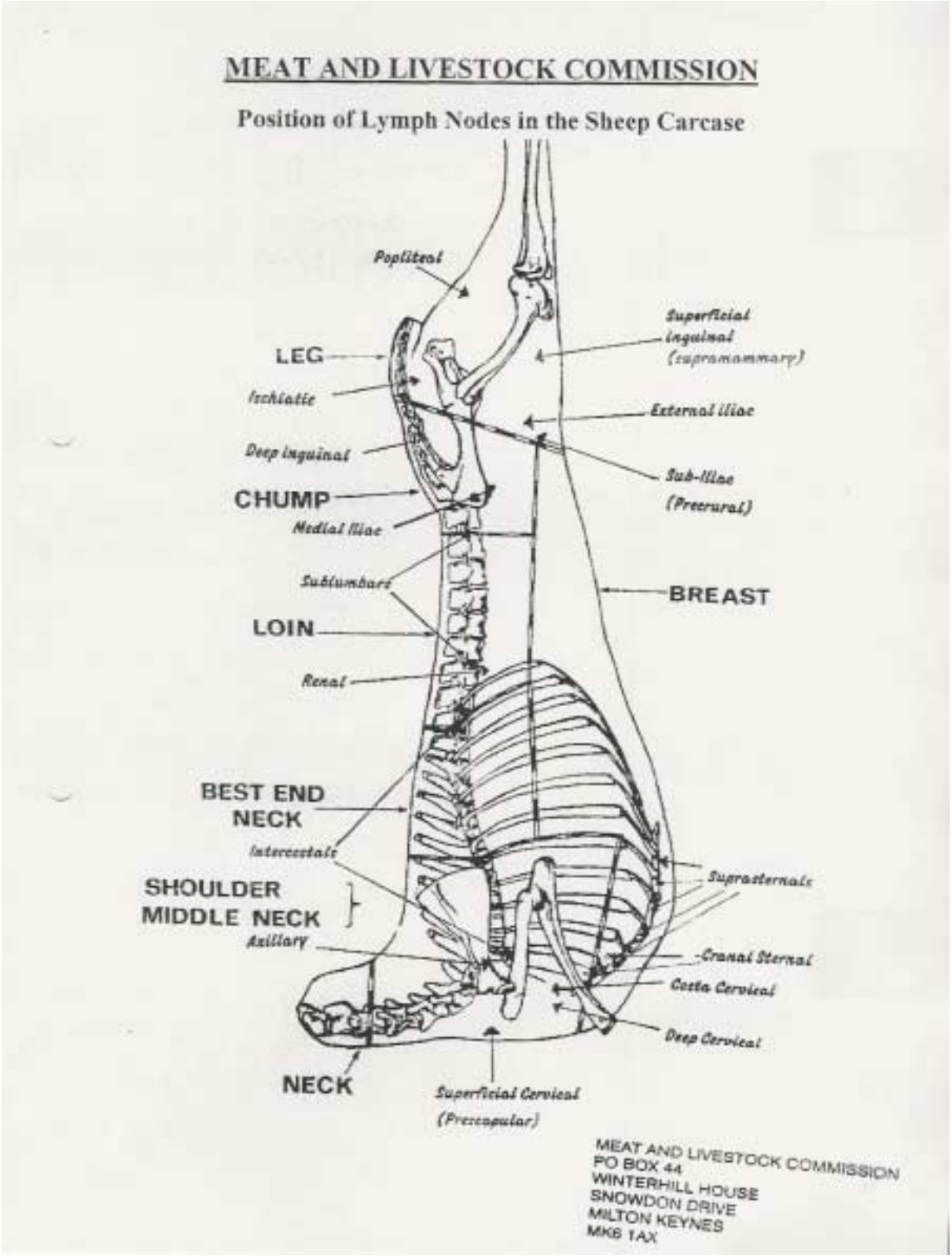
The Leatherhead report indicates that <0.1 kg out of 1 kg of stomach is used for food. It is thought that much of this would be for haggis manufacture. It is not known whether this is subject to any cleaning process that would remove possible infectivity, but it is assumed not.

5.4 Consumption of Infected Tissues

In "*Assessment of risk from Possible BSE Infectivity in Dorsal Root Ganglia"* (DNV, 1997a) it was assumed that only 5% of any infectivity present in meat sold to the consumer would be consumed. This recognised that DRG are located within the bone of the vertebral column and would often not be consumed. In a similar study recently carried out for the Food Safety Authority of Ireland a distribution of values with a normal distribution having a 95 percentile range from 5% to 95% was used.

Infectivity in a lamb or sheep carcase is widely distributed (e.g. that associated with lymph nodes). Whilst it is likely that less than 100% would be consumed (e.g. lymph tissue may be discarded with fat) there are no data on which to base any assumption. For the present it has been assumed that 100% of infectivity in meat sold to a consumer would be consumed.

Figure 5.1: Position of Lymph Nodes in the Sheep Carcase



6. ASSESSMENT OF EXPOSURE TO INFECTIVITY IN FOOD

6.1 Infectivity Scenarios

It is not known whether or not BSE infectivity is currently present in the UK sheep flock and if it were what the incidence might be. With this uncertainty, this study will be based on the premise that BSE infectivity is present in the UK sheep flock using a set of defined infectivity scenarios.

In Section 2.4 the number BSE cases in sheep was estimated assuming that sheep may have been infected with BSE from eating contaminated meat and bone meal in the early stages of the BSE epidemic. This indicated that the proportion of scrapie cases that were BSE would have been in the range 0.5% to 5% in 1990. As the number of cases would have been expected to fall following the ruminant feed ban in 1988, the following set of scenarios are proposed.

Case	% scrapie cases as BSE
Low	0.01%
Medium	0.10%
High	1.00%
Maximum	10.00%

6.2 Initial Exposure Estimates

The overall exposure of the UK population to BSE infectivity can now be estimated by combining the infectivity estimates (Table 4.1), with the development of infectivity by age (Table 3.3), and the inclusion rates in food (Table 5.2) for each tissue and age group. A worked example for one age group and scenario is shown in Figure 6.1 to illustrate clearly how the model works.

The risk is presented in terms of the expected consumption of infectivity in terms of human oral ID_{50} units. A worst case assumption would be that exposure to one human oral ID_{50} unit would result in a 50% chance of infection and similarly exposure to 0.1 of an ID_{50} would result in a risk of infection of 5%. This is based on the underlying assumption that there is a linear dose response relationship and that there is no safe threshold. This is likely to be very pessimistic, especially for very low exposures.

The model has been evaluated using a probabilistic risk assessment approach to reflect the uncertainties in some input parameters. Each main variable has been defined as a distribution of values and the result calculated many times using a Monte Carlo simulation tool (Crystal Ball, Decisioneering Inc). The values used for the input data are presented in Appendix 1. The simulation has been carried out using Latin Hypercube sampling with 10,000 iterations.

The results for the four infectivity scenarios are given in Table 6.1.

Table 6.1: Exposure of the UK Population to BSE Infectivity in Sheep Meat

Scenario Percentage scrapie as BSE	1 Low 0.01%	2 Medium 0.10%	3 High 1.00%	4 Maximum 10.00%
Total infectivity consumed by UK Population per year (human oral ID50 units)	0.35	3.5	35	350
2.5 percentile	0.002	0.02	0.2	2
97.5 percentile	65	650	6,500	65,000

The table gives the total exposure (median value) in terms of human oral ID_{50} units for each of the four scenarios together with the 2.5 and 97.5 percentile values. The distribution of infectivity by age group and tissue type is the same for each scenario and summarised in Table 6.2. this is colour coded to highlight the main risk contributors.

6.3 Discussion

The total infectivity consumed for each scenario in Table 6.1 is the total number of human oral ID_{50} units consumed by the whole UK population. When interpreting these results it is important to appreciate that they are based on the set of assumptions reported. It is essential that the assumptions and approach are critically reviewed before the results are used to inform any decisions.

The results for each scenario have a 95 percentile range of over 4 logs, largely due to the uncertainty in the species barrier. With this uncertainty, the results are best used as comparative indicators (e.g. in assessing the effect of alternative risk reduction measures) rather than as measures of absolute risk. The four scenarios cover a wide range of possible results, ranging from a relatively low level of risk in the Low Scenario to a fairly high level of risk in the Maximum Scenario. However, the risk levels are not so low that they could be judged to be clearly insignificant.

In Table 6.2 it is shown that about 75% of the total exposure is due to cull ewes, with about 20% from lambs over 6 months. However this will be very dependant on assumptions made about how infectivity develops through the incubation period. The Table also shows that 83% on the exposure is due to infectivity present in lymph tissues. A further 9% is due to intestines, utilised as natural casings for sausages.

Table 6.2: Contribution to Total Infectivity by Age Group and Tissue

	Lambs < 6 months	Lambs > 6 months	Hoggets > 1 year	Cull ewes	Total
Category 1					
Brain	0.03%	0.2%	0.0%	0.0%	0.2%
Spinal Cord	0.04%	0.3%	0.0%	0.0%	0.3%
Category 2					
Lymph nodes	2.1%	13.8%	0.3%	67.3%	83.4%
Spleen	0.0%	0.0%	0.0%	0.0%	0.0%
Tonsil	0.0%	0.0%	0.0%	0.0%	0.0%
Intestine	0.1%	4.6%	0.02%	4.5%	9.3%
Category 3					
Stomach	0.02%	0.1%	0.00%	0.5%	0.7%
Liver	0.10%	0.7%	0.01%	3.2%	4.0%
Thymus	0.05%	0.3%	0.01%	1.6%	2.0%
Category 4					
Heart	0.00%	0.01%	0.00%	0.05%	0.07%
Kidney	0.00%	0.01%	0.00%	0.05%	0.07%
Total	2.4%	20.0%	0.3%	77.3%	100.0%

Key:	
> 10%	
> 1%, < 10%	
> 0.1%, < 1%	

6.4 Risk Reduction Measures

An examination of the distribution of infectivity by age group and tissue type, as shown in Table 6.2, suggests a number of possible ways in which exposure to infectivity could be reduced. Possible risk reduction measures are defined below and their effectiveness evaluated using the exposure model.

RRM-1: No animals older than 1 year allowed in food for human consumption.

RRM -2: All lymph nodes removed from carcase as far as possible. It is assumed that 95% of the lymph tissue would be removed

RRM-3: Use of intestines banned a) from animals older than 1 year, and b) from all animals.

RRM-4: All offals (intestine, liver, thymus, stomach) from animals older than 1 year banned.

The estimated exposure to infectivity with these Risk Reduction Measures is shown in Table 6.3 for the Medium Scenario (0.1% scrapie cases are BSE). This shows the estimated exposure for RRM-1 and RRM-2 individually and for a number of combinations. RRM-3 and RRM-4 are only shown in combination with RRM-2, as it would not make sense to eliminate the risk from intestines without first eliminating the greater contribution from lymph nodes.

Table 6.3: Effectiveness of Risk Reduction Measures

Total exposure to BSE infectivity for Medium Scenario (0.1% scrapie as BSE)
Human oral ID_{50} units per year

Risk Reduction Measures	Median	95 percentile range		% reduction
		2.50%	97.50%	
Base Case	3.53	2.20E-02	650	
RRM-1	0.90	5.40E-03	174	75%
RRM-2	0.78	5.00E-03	140	78%
RRM-1 + RRM-2	0.31	1.90E-03	56	91%
RRM-2 + RRM-3a	0.62	3.90E-03	113	82%
RRM-2 + RRM-3b	0.42	2.70E-03	78	88%
RRM-2 + RRM-4	0.31	1.90E-03	56	91%
RRM-2 + RRM-3b + RRM-4	0.12	7.20E-04	23	97%

RRM-1: No animals older than 1 year allowed in food for human consumption.
RRM -2: All lymph nodes removed from carcase as far as possible. It is assumed that 95% of the lymph tissue would be removed
RRM-3: Use of intestines banned a) from animals older than 1 year, and b) from all animals.
RRM-4: All offals (intestine, liver, thymus, stomach) from animals older than 1 year banned.

Both RRM-1 and RRM-2 reduce the risk of exposure to infectivity by about 75%. By combining them the exposure is reduced by over 90%. A similar risk reduction is obtained by banning the use of all offals from animals over 1 year old (RRM-4) rather than banning the complete animals (RRM-1). The greatest risk reduction (97%) is obtained by combing

RRM3b (banning use of intestines from animals of all ages) with RRM-4 (banning the use of all offals from animals over 1 year old) and removal of all lymph nodes.

Another risk reduction measure proposed would be to screen sheep by genotype and only allow the most TSE resistant genotypes into food for human consumption. This should be effective in reducing exposure to TSE infectivity. This has not been assessed in this report as there were no data available for the prevalence of BSE in sheep of different genotypes and so the study was based on an assumed range of values for the overall prevalence.

6.5 Sensitivity Assessment

From the above, it is apparent that one of the key assumptions for this assessment is the rate of development of infectivity in lymph nodes. The base case assumes that at 6 months to one year infectivity is a factor of 10 less than for a clinical case based on Hadlow's 1982 results. Other studies (e.g Jeffrey *et al*, 2001) have reported signs of infection very early in the incubation period and it has been suggested that the level of infectivity could plateau early. A sensitivity case has therefore been defined with infectivity reaching 100% of the clinical level by the 6-12 month old group, and being a factor of 10 less (e.g.10%) for the less than 6 month group.

This case has then been re-evaluated for the medium scenario (0.1% scrapie cases as BSE). The median of the total infectivity consumed increases by a factor of just over two from 3.5 to 8.3 human oral ID_{50} units. RRM-1 (No animals older than 1 year allowed in food for human consumption) now reduces the risk by only 34%. RRM-2 (All lymph nodes removed) however, now reduces the risk by 88% to 1 human oral ID_{50} unit, only slightly greater than the risk for the base case with this risk reduction measure. The combination of RRM-1 and RRM-2 reduce the risk by 93%.

If infectivity grows more rapidly in lymph tissue than assumed for the base case then RRM-1 is less effective, but RRM-2 remains an effective risk reduction measure.

Figure 6.1: Worked Example
Infectivity consumed for Lambs < 6 months old for Scenario 2

Box 1: Incidence of BSE in Sheep Flock

Scenario	2: Medium	0.10% of scrapie cases are BSE
Incidence of scrapie in UK flock		0.10%
Lambs < 6months slaughtered		60% of 10,840,000
		6,504,000
Total number BSE +ve		6.5

The number of BSE +ve animals entering the food chain are calculated from the assumed proportion of scrapie cases as BSE and the total number slaughtered for each age group

Box 2: Infectivity of CNS Tissues

Infectious dose for cattle	50	Cattle oral ID50/g	Range: 10 - 1000
Cattle human species barrier	10		Range, 1 to 10,000
Infectivity to humans	5	Human oral ID50/g CNS tissue	

Box 3: Infectivity in one infected animal (lambs < 6 months)

		Relative Infectivity	Weight kg	% into food	Age factor	Reduction factor	Infectivity Consumed
Category 1							
	Brain	1	0.10	5.0%	0.01%	1	0.0025
	Spinal Cord	1	0.04	20.0%	0.01%	1	0.004
Category 2							
	Lymph nodes	0.1	0.04	100.0%	1.00%	1	0.2
	Spleen	0.1	0.10	0.0%	1.00%	1	0
	Tonsil	0.1	0.01	0.0%	1.00%	1	0
	Intestine	0.1	1.20	90.0%	1.00%	400	0.0135
Category 3							
	Stomach	3.0E-04	1.00	10.0%	1.00%	1	1.5E-03
	Liver	3.0E-04	0.61	100.0%	1.00%	1	9.2E-03
	Thymus	3.0E-04	0.30	100.0%	1.00%	1	4.5E-03
Category 4							
	Heart	3.0E-05	0.20	50.0%	1.00%	1	0.00015
	Kidney	3.0E-05	0.10	100.0%	1.00%	1	1.58E-04
Total	(Human oral ID50 units per infected animal)						0.24

The infectivity consumed in one infected animal is calculated for each tissue. The infectivity to humans from Box 2 is multiplied with the relative infectivity (Table 4.1), the weight and inclusion in food (Table 5.2) the age factor (Table 3.3) and any reduction factor.

Box 4: Total Infectivity Consumed

Total infectivity consumed by UK population 1.53 Human oral ID50 units per year

The total infectivity consumed for each age group is then the total infectivity for one infected animal from Box 3 multiplied by the number of BSE +ve cases for that group from Box 1.

7. REFERENCES

Diringer, H., (1999) *Bovine spongiform Encephalopathy (BSE) and Public Health.* In Aggett, P.J., Kuiper,H.A., (Eds) 1999. Risk Assessment in the food chain of children. Nestlé Nutrition Worksop Series, **44**, 225-233. Nestlé Ltd,, Vevey/Lippncott Williams & Wilkins Publishers, Philadelphia.

DNV (1997a): "*Assessment of risk from Possible BSE Infectivity in Dorsal Root Ganglia*", Report to the Ministry of Agriculture Fisheries and Food and the Spongiform Encephalopathy Advisory Committee, Det Norske Veritas C7831, December 1997.

DNV (1997b): "*Overview of Risks from BSE via Environmental Pathways*", Report to Environment Agency, Det Norske Veritas C7243, June 1997.

DNV (1998a) *Assessment of Exposure to BSE Infectivity in the UK Sheep Flock.* Report for The Meat and Livestock Commission, DNV Report No. C782506, Rev 2 July 1998.

DNV (1999)) *Assessment of Exposure to BSE Infectivity in the Cattle Herd.* Report for The Meat and Livestock Commission, DNV Report No. C78250601, Rev 0 February 1999.

Foster. JD, Bruce, M McConnell, I, Chree, A And Fraser, H. (1996) *Detection of BSE Infectivity in Brain and Spleen of Experimentally Infected Sheep,* Veterinary Record, **138**, 546-548.

Foster, JD Parnham, DW, Hunter, N and Bruce, M (2001) *Distribution of the Prion Protein in Sheep Terminally Affected with BSE Following Experimental Oral Transmission.* Journal of general Virology, **82**.

Hadlow, WJ, Kennedy, RC, and Race, RE (1982) *Natural Infection of Suffolk Sheep with Scrapie Virus.* Journal of Infectious Diseases, **146**, No 5, 657-664.

Hadlow, WJ, Race, RE, Kennedy, RC and Eklund, C,M (1979) *Natural Infection of Sheep with Scrapie Virus.* In Slow transmissible Diseases of the Nervous System, Vol 2, 3-12, Ed by SB Prusiner & WJ Hadlow. New York, Academic Press.

Hoinville LJ, McLean AR, Hoek, AR, Gravenor, MB, Wilesmith J (1999) *Scrapie occurrence in Great Britain.* The Veterinary Record **145** 405-6

Hoinville LJ, Hoek, AR, Gravenor, MB, McLean AR (2000) Descriptive Epidemiology of scrapie in Great Britain: Results of a postal survey. The Veterinary Record **146** 455-61.

Jeffrey, M, Ryder, S, Martin, S, Hawkins, SAC, Terry, L, Berthelin-Baker, C and Bellworthy, SJ, (2001) Oral Inoculation of Sheep with the Agent of Bovine Spongiform Encephalopathy (BSE). 1. Onset and Distribution of Disease-specific PrP Accumulation in Brain and Viscera. Journal of Comparative Pathology, **124**, 280-289.

Leatherhead Food RA (1997) *Audit of Bovine and Ovine Slaughter and By-products Sector* MAFF Project No. SE0217, by Leatherhead Food Research Association and the Meat and Livestock Commission.

SEAC (1994) *Transmissible Spongiform Encephalopathies: A Summary of Present Knowledge and Research.* HMSO, London.

Scientific Steering Committee, EC (2000) *Opinion: Oral Exposure to Humans of the BSE Agent: Infective Dose and Species Barrier* Adopted by the SSC at its meeting on the 13th - 14th April 2000.

Van Keulen, LJM, Schreuder, BEC, Vromans, MEW, Langeveld, JPM & Smits, MA. (2000) *Pathogenesis of natural scrapie in sheep.* Archives of Virology, **16**, 57-71.

APPENDIX I

MODEL INPUT DATA

The variables shown below have been assigned distributions as input to the Monte Carlo simulation. All other variables have fixed values as given in the report.

Crystal Ball Report
Simulation started on 01-10-7 at 20:18:35
Simulation stopped on 01-10-7 at 20:19:03

Assumptions

Assumption: Infectious dose for cattle

Lognormal distribution with parameters:	
Geometric Mean	50.00
95% - tile	1,000.00

Selected range is from 10.00 to 1,000.00
Mean value in simulation was 147.09

Assumption: Cattle human species barrier

Custom distribution with parameters:		Relative Prob.
Single point	1.00	0.010000
Single point	10.00	0.250000
Single point	100.00	0.250000
Single point	1,000.00	0.250000
Single point	10,000.00	0.240000
Total Relative Probability		1.000000

Mean value in simulation was 2,677.51

Assumption: Percent spinal cord in food (lamb)

Normal distribution with parameters:	
5% - tile	15.0%
95% - tile	25.0%

Selected range is from -Infinity to +Infinity
Mean value in simulation was 20.0%

Assumption: Percent stomach in food

Normal distribution with parameters:
Mean 10.0%
Standard Dev. 1.0%

Selected range is from -Infinity to +Infinity
Mean value in simulation was 10.0%

Assumption: Reduction factor for cleaning intestines

Lognormal distribution with parameters:
Geometric Mean 100.00
95% - tile 200.00

Selected range is from 0.00 to +Infinity
Mean value in simulation was 109.27

Assumption: Age .01%

Lognormal distribution with parameters:
Geometric Mean 0.01%
95% - tile 0.10%

Selected range is from 0.00% to +Infinity
Mean value in simulation was 0.03%

Assumption: Age 0.1%

Lognormal distribution with parameters:
Geometric Mean 0.10%
95% - tile 1.00%

Selected range is from 0.00% to +Infinity
Mean value in simulation was 0.26%

Assumption: Age 1%

Lognormal distribution with parameters:
Geometric Mean 1.00%
95% - tile 10.00%

Selected range is from 0.00% to +Infinity
Mean value in simulation was 2.67%

Assumption: Age 10%

Lognormal distribution with parameters:
Geometric Mean 9.95%
95% - tile 20.00%

Selected range is from 0.00% to +Infinity
Mean value in simulation was 10.89%

Assumption: Age 50%

Lognormal distribution with parameters:
Geometric Mean 50.00%
95% - tile 100.00%

Selected range is from 0.00% to +Infinity
Mean value in simulation was 54.63%

End of Assumptions

APPENDIX II

LIST OF MAIN ASSUMPTIONS

LIST OF MAIN ASSUMPTIONS

The main assumptions made in the assessment are summarised here to facilitate review.

1. Scrapie incidence: The average incidence of scrapie in the UK flock is assumed to be 0.1%
2. BSE in Sheep: The incidence of BSE in sheep in the UK lies within the range of the four scenarios assumed; i.e 0.01% to 10% of scrapie cases are BSE.
3. The relative infectivities of different tissues in a sheep with BSE will be similar to those for scrapie as reported by Hadlow (1982) and presented in the SEAC (1994) report. These are summarised in Table 4.1.
4. The infectivity of CNS tissue in a sheep with BSE as an oral dose to humans will be assumed to be the same as the infectivity of the CNS tissue of a cow with BSE.
5. The infectious dose for cattle is assumed to be 50 cattle oral ID_{50} /g, with a range from 10 to 1000 (Section 4.1.1)
6. Species barrier: the species barrier between BSE in cattle (and sheep) and humans is represented as a distribution using values of 10, 100, 1000 and 10,000 with equal probabilities, and a 1% probability of it being 1.
7. Infectivity development with age: the relative infectivity of each potentially infected tissue as percent of the infectivity in a fully infected animal are as given in Table 6.1.
8. The main tissues that could contain BSE infectivity and be present in food for human consumption are as listed in Table 5.2. This table also provides estimates of the weight of each tissue in a typical carcase and the percentage of this included in food
9. The processing of sheep intestines for use as natural sausage casings is assumed to remove most of the attached lymph tissue, and reduce the infectivity by a factor of 100.
10. It is assumed that 100% of the infectivity present in any food tissue is consumed.