Introduction

1. An ad hoc group of experts was convened to consider the implications of BSE and produced a report (59 SG/13/CS 4B) in September 1990 which was adopted by the 59th General Session. The 59th General Session resolved in addition that a draft chapter on BSE should be prepared for the OIE International Animal Health Code.

2. The purpose of the present document is to take account of developments since 59 SG/13/CS 4B was prepared, and to provide supporting information relevant to the BSE chapter (3.2.13.) of the OIE International Animal Health Code.

Development of the epidemic

3. BSE was first recognised in Great Britain in November 1986, although evidence collected later indicated that the first clinical cases had occurred in April 1985 (49,54). Initial epidemiological studies indicated an extended common source epidemic in which all affected animals were index cases (54). Epidemiological studies considered a wide range of possible causative factors which might provide a common link between cases (use of therapeutic and agricultural chemicals, and biological products; introduction via imported animals, semen or animal products; transmission of the agent directly or indirectly on farms which also had sheep). The results of these studies, together with the disease's similarity with scrapie, identified the exposure of cattle to the agent of a transmissible spongiform encephalopathy (TSE) through feed containing ruminant-derived protein in the form of meat and bone meal as the likely source of the disease (51,54). The role of meat and bone meal is strongly supported by the results of a case-control study (52). Two possible hypotheses as to the origin of this agent were consistent with the epidemiological findings: either that it was the agent of scrapie itself, or that it was a cattle-adapted strain of a TSE agent (51).

4. Computer simulations indicate that exposure to the agent sufficient to give rise to clinical disease began abruptly in 1981/2 (51,54). The key factor appears to be the timing of certain changes in rendering
practice in the United Kingdom which were coincident with this increase in exposure, although other risk factors are also clearly relevant, notably the relationship between numbers of cattle and sheep (on which will depend the proportion of meat and bone meal represented by sheep material) and the prevalence of scrapie (51,54).
5. Epidemiological studies indicate that the majority of BSE infected animals have been exposed in calfhood (54). It is predominantly animals in dairy herds that are affected (54). At 6 September 1991 the confirmed dairy herd incidence was 26.65% and the beef suckler herd incidence was 2.98%. Over 80% of the cases in beef suckler herds occurred in cows that originated from (and, presumably, were exposed in) dairy herds. The age of peak incidence is four to five years and the incubation period varies from 2.5 to at least eight years (54). The rate at which cases have been reported has increased since 1986. A marked increase in the incidence of clinical disease which occurred in 1989 can be explained by the recycling into the cattle population through meat and bone meal of material from cattle which themselves were infected (53).

Further epidemiological studies have confirmed the hypothesis of a common source epidemic having arisen because of exposure through feed (51). To the end of July 1991 only one case had been reported which could not be explained by exposure to infected feed (5). This animal, born in November 1988, was the offspring of a cow which developed BSE three months after giving birth, and may be a case of maternal transmission. However, to the end of July none of 316 offspring of BSE infected cows being observed under controlled conditions had developed disease, although some were nearly four years old. Even if maternal transmission were to occur, the disease would still die out if cattle are no longer exposed to the agent through feed, because the necessary contact rate of at least 1:1 would not be maintained (50).

6. Important conclusions can be drawn from the information set out in paragraphs 3-5 above:

6.1. there is strong evidence that infected feed is the cause of the disease (51,54);

6.2. there is evidence that other methods of exposure are not likely to be important in the spread of disease. The evidence currently available therefore suggests:
   - that it is unlikely that animals not exposed to contaminated feed would develop the disease;
   - that the risk of an animal developing disease depends upon exposure, not upon the past or present BSE status of the herd to which the animal belongs; and

6.3. because of the long incubation period of the disease, it is possible for infection to be recycled in animal feed before a significant number of clinical cases have occurred; and

6.4. even if the source of infection is cut off, new cases can be expected to emerge for several years, after which the incidence of disease is likely to fall markedly.
Geographical Incidence

7. The number of cases of BSE in different countries by date of clinical onset in each year is described in Table I, and the annual incidence of BSE is described in Table II.

Table I

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Adult &gt;2 yrs Cattle population (Thousands ) 1990</th>
<th>Number of cases</th>
<th>1987 and before</th>
<th>1988</th>
<th>1989</th>
<th>1990</th>
<th>1991*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (of which Northern Ireland)</td>
<td>4,449 ** (516) **</td>
<td></td>
<td>473</td>
<td>3,049</td>
<td>7,648</td>
<td>14,471</td>
<td>24,210</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>3,615</td>
<td></td>
<td></td>
<td>15</td>
<td>14</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>953</td>
<td></td>
<td></td>
<td>2</td>
<td>8</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>France</td>
<td>12,100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Provisional figures  ** Breeding cattle only

Table II

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (Northern Ireland)</td>
<td>4,449 ** (516) **</td>
<td></td>
<td>0.011</td>
<td>0.0069</td>
<td>0.17</td>
<td>0.33</td>
<td>0.54</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>3,615</td>
<td></td>
<td>0.0004</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0005</td>
<td>0.0008</td>
</tr>
<tr>
<td>Switzerland</td>
<td>953</td>
<td></td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0003</td>
</tr>
<tr>
<td>France</td>
<td>12,100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Provisional figures  ** Breeding cattle only
Appendix Vb (contd)

In addition, two and one cases respectively have been reported in Oman (10) and the Falkland Islands, although these were imported from Great Britain. On the basis of the data above, the United Kingdom is at present the only country where the incidence of BSE is regarded as high. France, Switzerland and the Republic of Ireland are regarded as having a low incidence.

8. Within the United Kingdom, incidence is higher in the South of England than elsewhere (51,54). This is due in part to the geographical distribution of rendering plants that had ceased to use processes, such as solvent extraction and the re-processing of greaves, which either destroy infectivity or significantly reduce the titre. In addition, there are likely to have been regional variations in the amount of infected sheep material entering different rendering plants, and in the use of meat and bone meal in concentrated feeds or in protein supplements. Incidence is substantially less in Northern Ireland (14).

Nature of the disease

9. In addition to the strong evidence that BSE arises from exposure of cattle to the agent causing scrapie or to a cattle-adapted form of it there are very close similarities between BSE and scrapie (49). BSE resembles scrapie in its long incubation period, symptomatology, age incidence and progression. The nature of the pathological lesions is very similar to that found in scrapie, and indeed the other spongiform encephalopathies in other species. As with the related disorders, there are characteristic spongiform changes in particular areas of the brain which are visible by light microscopy (49). Detergent-treated extracts of affected bovine brain yield scrapie associated fibrils (SAF) visible by electron microscopy (49). These fibrils contain a modified host-coded protein (PrP) which is the bovine homologue of the fibril protein obtained from the brains of sheep with scrapie (26). There is no epidemiological evidence for the direct spread of infection between cattle, suggesting that BSE is not highly contagious. Certain laboratory strains of mice injected intracerebrally and intraperitoneally with BSE-affected brain have developed spongiform encephalopathy after the expected incubation period of many months (17). Bioassay in laboratory species such as mice is at present the only way of measuring BSE infectivity. In mice, the disease looks and behaves like experimental mouse scrapie. As with scrapie, the transmission of BSE to mice has also been accomplished by feeding affected brain (2,3). BSE has also been transmitted to cattle by combined intracerebral and intravenous injection of affected brain (12).

10. It can therefore be concluded that:

10.1. BSE is indisputably a member of the group of TSEs, of which scrapie is the prototype.
10.2. hypotheses about the way in which BSE will behave biologically can be based on what is known about scrapie, even though it is unlikely that BSE will resemble scrapie in every respect.
Transmission of BSE

11. The best understood naturally occurring diseases in the same category as BSE and scrapie are set out in the table at Annex 1. Experimental transmissibility is a key factor in the definition of these diseases. The mechanisms by which transmission occurs naturally vary with the disease, but conclusions about the risks of transmission to both animals and man can still be drawn from an understanding of the relevant factors:

11.1. Route of transmission

The oral route has been shown experimentally to transmit BSE (2,3), scrapie (41,42), TME (33), kuru (18), CJD (18), and it plays a role in the natural transmission of all these diseases except CJD. However, compared to parenteral exposure, ingestion is a relatively inefficient route of transmission in all the TSEs that have been studied experimentally. For mouse scrapie, the oral dose required is about a hundred thousand times greater than the intracerebral dose (29,30). In limited studies of BSE, the amount of affected cattle brain required to produce the disease in mice was between a thousand and a million times greater by the oral route than by intracerebral injection (2,3,17).

11.2. Species barrier

There is no known causal association between scrapie in sheep or goats and spongiform encephalopathies in man. The incidence of CJD (see also Annex 1) in many countries of the world is independent of the presence of sheep, natural scrapie (or any other animal disease) and the use of sheep products in human food. Likewise individuals with CJD show no particular occupational or other exceptional exposure to sheep or sheep products (6). CJD has been observed in a lifelong vegetarian (34), and has an average incidence that is no higher in countries with a recent relatively high incidence of scrapie, such as Great Britain, than in other countries. Spongiform encephalopathies transmit more readily to animals of the same species than to other species. BSE has been transmitted experimentally to mice (2,3,17), goats (37), sheep (37) and pigs (13). But such experimental cross-species transmissions require high dose, and usually parenteral exposure. With repeated experimental passage in the new host, the incubation period usually becomes shorter (28). Experiments have confirmed that BSE behaves in the expected way.

11.3. Dose

Transmission of spongiform encephalopathies is dependent on the size of the infective dose.
11.4. Tissue distribution of the agent

The points covered in 11.1 - 11.3 above are relevant to any possible risk to animals of the same species, of different species, and to man, from exposure to the BSE agent. Clearly, there would be little or no risk of infection as a result of oral exposure to tissues which contain no detectable infectivity as determined experimentally using the most efficient routes of inoculation. There is a large literature on the amounts of infectivity in different tissues of animals and man infected experimentally or naturally with one or other of the TSE agents. Although the general patterns are similar, the amounts of infectivity in tissues vary with the different diseases. Data obtained from studies of natural scrapie in Suffolk sheep (21, 24) and goats (22) are particularly valuable in making "worst-case" predictions of the potential risks due to BSE from various bovine tissues. The pattern seen with natural scrapie, based on extensive studies summarised in Annex 2a and 2b, is described in the next paragraph.

11.4.1. Development of natural scrapie in sheep and goats

No agent was detected in any tissue from lambs of up to 8 months of age (21,24). At 10-14 months of age low infectivity was present in the large masses of lymphoreticular tissue in the intestines (Peyer's patches), lymph nodes associated with the gastro-intestinal tract and elsewhere, spleen and tonsil (21,24). The titres in these tissues increased subsequently and, before clinical signs appeared, infectivity was detected in the spinal cord, medulla and some other areas of the brain (21,24). By the time animals showed clinical disease, levels of infectivity in the central nervous system, including the spinal cord, had risen above those in the lymphoreticular system (21,22,24).

11.4.2. Non-infectious tissues in natural scrapie in sheep and goats

Attempts have been made to detect scrapie infectivity in a wide range of other tissues. Those which have not been shown to harbour detectable infection by bioassay methods include:

- skeletal muscle (ie carcase meat) (21,22,24)
- heart (21,24)
- kidney (21,22)
- milk and colostrum (21,22)
- mammary gland (21,22,24)
- uterus (21,22,24)
- ovary (21,22,24)
- seminal vesicle and testis (21)
- blood (21, 22, 24)
- saliva (21, 22)
- skin (46)
11.4.3. Tissue distribution of agent in BSE

Transmission experiments in mice have been undertaken with a wide range of tissues from confirmed cases of BSE. So far, BSE infection has been transmitted, by feeding (2,3) or by injection (12,17,37), only by brain. Other experiments have involved periods of observation of two years or more - i.e. near to the mouse's natural lifespan, and more than twice the maximum period required for disease to be transmitted by brain. In these experiments, milk and mammary gland (2,3); placenta (2,3); lymph nodes (2,3) and spleen (2,3) have failed to transmit the disease through oral challenge, or even to establish subclinical BSE infection of the lymphoreticular system. Furthermore, mice exposed parenterally to spleen, placenta, skeletal muscle, buffy coat, semen (38) and bone marrow did not succumb to disease.

11.5. Maternal transmission

As indicated above (paragraph 5 and 6.2) field and experimental experience with live cattle suggests that transmission from cow to calf is not likely to be a factor in the development of BSE (50). This is in marked contrast to scrapie, but is consistent with the situation with natural TME (23) and kuru, which are both "dead-end" diseases. The data summarised in 11.4.3 above suggest that the BSE agent is concentrated in the brain in clinical cases and that if it is present outside the CNS it will be in much lower amounts (2,3). This follows the pattern of transmissible mink encephalopathy where maternal transmission does not occur (23). In natural sheep scrapie the lymphoreticular system contains high levels of infectivity, (21,24) placenta from affected sheep can experimentally transmit disease following oral exposure of sheep and goats (41,42), and on present evidence the transmission of scrapie by embryo transfer cannot be ruled out.

12. The conclusions emerging from these considerations are:

12.1. the risk of infection with BSE, if any, arises only from exposure to certain tissues of infected animals, or products prepared from those tissues.
12.2. In affected animals, the analogy of scrapie suggests that significant infectivity is likely to be present only in the central nervous system, and certain tissues in the lymphoreticular system. The evidence from experience to date indicates that the distribution of infectivity in BSE cases is probably more restricted than in scrapie.

12.3. By analogy with scrapie, detectable infection will not be found anywhere in an animal incubating the disease until it is several months old, even if it was infected at or before birth.
12.4. Furthermore, there is a range of tissues in which no detectable infectivity is expected to occur at any time, even in clinically affected animals. These tissues include:

- Carcase meat
- Milk
- Hides
- Skins
- Semen

12.5. Tissue infectivity studies so far support the hypothesis that maternal transmission is not likely to be a significant factor in the transmission of BSE. Nevertheless, the single case cited in paragraph 5 above suggests that maternal transmission cannot be completely ruled out in individual cases.

Qualities of the Agent

13. Infection with these agents does not provoke a detectable immunological reaction so there is at present no practical means of detecting infection in healthy animals. The agents causing scrapie, and by inference BSE, are exceptionally resistant to heat, ultraviolet and ionising radiation, and chemical disinfection (47,48). Wet heat (31) inactivates more effectively than dry heat (8,9,47,48). The method used in the United Kingdom of inactivating the CJD agent in hospitals and laboratories is based on studies of the scrapie agent. It involves porous load autoclaving at 134°-138° for 18 minutes at 30 p.s.i. or 207 hPa (hold temperature and time) (15). Two percent available chlorine acting for 1 hour is effective (9,29,48) and a useful alternative disinfectant is 1 N (four percent) sodium hydroxide acting for 1 hour (47,48). However, it is possible that BSE is caused by a relatively thermostable strain of agent, and in the absence, so far, of specific information on the BSE agent, it is not possible to guarantee that any particular type of treatment will completely inactivate it, especially under the conditions of commercial rendering.

Precautions

14. The action which should be taken by countries with regard to BSE should be based on the conclusions set out above. The main risk factors to be considered are:

- the use of ruminant protein (excluding milk) in ruminant feed
- systems of rendering and other methods of animal waste disposal
- the existence of measures to avoid or reduce exposure to potentially infected material
- the presence of scrapie
- the size of the sheep population, absolutely and relative to that of cattle
- routes of exposure
Action should be designed to distinguish between the risks to animal and public health, and falls into four categories: (Paras 14.1-14.4)

14.1. **Surveillance**

Because of the long incubation period of the disease and the absence of any detectable serological or other tests for infection, animals could be incubating the disease, even in countries which have now taken precautions (4) such as those outlined below. It is therefore important to:

14.1.1. ensure farmers, veterinarians and the national Veterinary Services are aware of the clinical signs;
14.1.2. ensure pathologists have the knowledge, experience and techniques to confirm the disease to a common standard and consider BSE as a differential diagnosis in all nervous diseases in cattle, including rabies; and

14.1.3. make suspicion of BSE notifiable.

14.2. Control of the disease where it is present

In the absence of clear evidence about the treatment needed to remove or inactivate the BSE agent, the key requirement is to eliminate the possibility that cattle might be exposed to the agent through their feed. On the basis that the feed route is the only significant factor in the development of the epidemic, this should be enough to ensure the disappearance of the disease. In the United Kingdom (5,40), Republic of Ireland and Switzerland, this requirement has been implemented by means of a ban on the feeding to ruminants of all protein material, other than milk, derived from ruminants. Such a measure would protect deer and other ruminant species from exposure to infection through food. In addition, the existence of such a ban in an exporting country would mean that trade restrictions on exports of ruminant species were not justified on account of BSE. In France there is a ban on the feeding of ruminant protein to cattle. Although transmission from cow to calf is not likely to be a significant factor, measures should be taken to isolate any suspect cases which are giving birth, to dispose of placenta safely and to cleanse and disinfect the isolation accommodation in order to minimise the risk of transmission.

14.3. Avoiding the occurrence of BSE in a country where disease has not been recognised

Because of the long incubation period of the disease, the agent may be present in those countries where the relevant risk factors exist, without having caused a sufficient number of clinical cases to be recognised. The recycling of undetected infection through cattle feed could already be taking place in such countries. Therefore, in countries where BSE has not been recognised, whenever possible:

14.3.1. studies should be undertaken to determine the extent to which the risk factors are present e.g. the occurrence and incidence of scrapie, the method of disposal of ruminant wastes and the origin, use of and inclusion rate of ruminant protein in rations fed to ruminants;

14.3.2. consideration might also be given to exclusion from ruminant rations of those tissues which, in sheep affected with scrapie or cattle infected with BSE,
are most likely to contain high titres of the agent (see 14.4 below). In a number of countries this has been implemented by means of a ruminant protein ban like that described in paragraph 14.2 above.

14.4. **Eliminating any risk that man, or other species, might be infected**

Measures to deal with any theoretical risk of BSE causing disease in man should take account of evidence about the tissue distribution of infectivity (see 11.4 above), and potential routes of infection (11.1). Countries may also want to consider supplementary measures which while not fully justifiable on scientific grounds should provide extra guarantees to their own and overseas consumers.
14.4.1. Animals exposed to infection through feed are those most likely to present a risk of carrying infection themselves. Infection is unlikely to be detectable in an animal which is incubating BSE before it is six months old (21, 24). Any detectable infectivity in older animals is likely to be confined to the central nervous system or lymphoreticular system. Restrictions to minimise any risk to man or other species should therefore apply to the following tissues (the "specified offals" (40)) from animals over 6 months old, and protein material derived from them:

- brain, spinal cord, tonsil, thymus, spleen and intestines (from duodenum to rectum inclusive).

14.4.2. Such restrictions should be considered where there is a high incidence of disease, or where the risk factors suggest that a substantial number of cases might arise. Additional reassurance could be provided by the removal from meat, where possible, of visible nervous and lymphatic tissue during the cutting process. Clearly, more of such tissue can be removed in the preparation of de-boned meat; the removal of the tissues from bone-in meat traded internationally would be a matter for the importing country.

14.4.3. Because of the greater efficiency of transmission by parenteral exposure (see 11.1) than via the alimentary tract (29,30), any risk that exists will be greater with materials which might be inoculated, intentionally or accidentally. This factor needs to be taken into account in reaching decisions about sourcing bovine material for the manufacture of products for veterinary and human medical use, and in offering advice on hygienic practices to workers in sectors where inoculation might occur.

14.4.4. Countries where BSE has occurred have taken various additional measures:

- compulsory slaughter of suspect cases, with total destruction of carcasses (UK (40), Switzerland, France, and Republic of Ireland);

- non-marketing of milk from suspect cases (UK) (39,40);

- voluntary slaughter arrangements for herds in which BSE cases occur (France, Republic of Ireland).
These measures are designed to serve mainly as a reassurance to domestic consumers.

RELATIONSHIP BETWEEN THE SUPPORTING DOCUMENT AND THE BSE CHAPTER IN THE CODE

15. The Code Chapter on BSE was drawn up bearing all the above scientific information in mind. Annex 3 shows which paragraphs of this supporting document provide the basis for each Article of the Code Chapter.
### Annex 1

Naturally-occurring transmissible spongiform encephalopathies

<table>
<thead>
<tr>
<th>HOST</th>
<th>DISEASE</th>
<th>REPORTED DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>Kuru</td>
<td>Papua New Guinea</td>
</tr>
<tr>
<td></td>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>(Iatrogenic, Sporadic, Familial)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gersmann-Sträussler (Scheinker) syndrome (GSS)</td>
<td>Familial, worldwide, but extremely rare</td>
</tr>
<tr>
<td>Sheep/Goats</td>
<td>Scrapie</td>
<td>Widely distributed</td>
</tr>
<tr>
<td>Mule deer</td>
<td>Chronic Wasting Disease (CWD)</td>
<td>North America</td>
</tr>
<tr>
<td>Elk</td>
<td>Transmissible Mink Encephalopathy (TME)</td>
<td>North America</td>
</tr>
<tr>
<td>Farmed mink</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>Bovine Spongiform Encephalopathy (BSE)</td>
<td>Europe</td>
</tr>
<tr>
<td>Cat</td>
<td>Feline Spongiform Encephalopathy (FSE)</td>
<td>See para 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK</td>
</tr>
</tbody>
</table>

**Creutzfeldt-Jakob Disease (CJD)**

CJD occurs worldwide at an incidence of about 1 case per million per annum (7). However, there have been rare instances of geographical clustering of cases where the annual incidence has been 30 times or more of this norm. Such clusters have been found in Israel (36) and Czechoslovakia (35). They are clearly related to the presence of point mutations at codon 200 of the PrP gene (19,20). Up to about 15% of all CJD cases are familial and some of these are associated with a variety of other mutations in the PrP gene. The great majority of cases (>85%) occur sporadically. A tiny proportion of these cases are iatrogenic. Epidemiological studies in many countries (including France (7,11) and the UK (25)), have shown that sheep are not a significant reservoir of infection causing CJD, and there is no evidence that CJD has an origin in any animal disease. Any hypothetical risk from bovine tissues used in pharmaceutical preparations, and sourced from countries, regions or herds where BSE exists, is eliminated by following the guidelines given in the Code (also see paragraph 14.4.3 of this document).
Feline spongiform encephalopathy (FSE)
FSE was first reported in a domestic cat in England in May 1990 (55). To the end of October 1991 23 cases have now been reported in the UK. The clinical and pathological features in five of these have been described (56). The presence of SAF's (43) and transmission of disease to mice following parenteral inoculation of brain tissue from an affected cat (5,38) has confirmed FSE is a member of the naturally occurring TSE group of diseases and is therefore listed in the table above.

Spongiform encephalopathy in exotic ungulates
In addition to the diseases listed above, naturally occurring spongiform encephalopathies have been identified in five species of exotic ungulates that were kept in zoos or wildlife parks in Britain (1,16,32). These animals were fed the same type of concentrated feeds that caused BSE, but the apparently shorter incubation periods in the zoo animals suggest that they were more susceptible to infection than cattle. Transmission of disease from the formalin-fixed brain tissue of a nyala and greater kudu to mice has been achieved (5, 38). All five species of these exotic ungulates belong to the Family Bovidae and are more closely related phylogenetically to cattle, sheep and goats (also Family Bovidae), than they are to deer (Family Cervidae).

Spongiform encephalopathy (SE) or SE-like lesions in other species
Ostriches kept in Germany in zoos showed lesions of spongiform encephalopathy (44,45). It will not be proved that the disease in ostriches is a TSE until transmission, the presence of scrapie-associated fibrils, and abnormal PrP are shown. There is therefore doubt at present as to whether infection with a TSE agent is the cause of the disease in ostriches.

White tigers kept in a zoo in Britain were reported in 1978 to show encephalopathy lesions which included spongiform degeneration, and which were positively associated with hepatic disease (27). Transmission studies gave negative results in mice and non-human primates. It is therefore concluded this is not a scrapie-like disorder.
Annex 2

a) Scrapie infectivity titres in tissues from naturally infected sheep and goats with clinical disease

<table>
<thead>
<tr>
<th>TISSUES</th>
<th>SHEEP (mean ± SEM of (n) samples)</th>
<th>GOATS (34-57 months)</th>
<th>(38-49 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category I (Central nervous system - CNS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cerebral cortex</td>
<td>4.4 ± 0.6 (9)</td>
<td>6.1 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>- corpus striatum</td>
<td>4.4 ± 0.4 (8)</td>
<td>5.6 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td>- diencephalon</td>
<td>6.0 ± 0.3 (8)</td>
<td>6.7 ± 0.4 (3)</td>
<td></td>
</tr>
<tr>
<td>- midbrain</td>
<td>6.1 ± 0.4 (8)</td>
<td>7.2 ± 0.4 (3)</td>
<td></td>
</tr>
<tr>
<td>- medulla oblongata</td>
<td>5.8 ± 0.2 (8)</td>
<td>6.6 ± 0.4 (3)</td>
<td></td>
</tr>
<tr>
<td>- cerebellar cortex</td>
<td>6.2 ± 0.6 (9)</td>
<td>6.9 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cervical</td>
<td>5.4 ± 0.3 (9)</td>
<td>5.8 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td>- lumbar</td>
<td>...</td>
<td>6.3 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Category II (Lymphoreticular system - LRS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- bronchial mediastinal (BM)</td>
<td>4.5 ± 0.2 (9)</td>
<td>5.0 ± 0.1 (3)</td>
<td></td>
</tr>
<tr>
<td>- mesenteric-portal (MP)</td>
<td>4.7 ± 0.1 (9)</td>
<td>4.8 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>- prescapular (PreS)</td>
<td>3.7 ± 0.4 (9)</td>
<td>4.8 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>- prefemoral (PreF)</td>
<td>4.0 ± 0.1 (9)</td>
<td>4.7 ± 0.5 (3)</td>
<td></td>
</tr>
<tr>
<td>- retro/supra-pharyngeal (R/S-P)</td>
<td>4.1 ± 0.2 (9)</td>
<td>5.0 ± 0.1 (3)</td>
<td></td>
</tr>
<tr>
<td>- supramammary</td>
<td>&lt;2.5 ± 0.4 (9)</td>
<td>4.7 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>Ileum (Peyer's patches)</td>
<td>4.7 ± 0.1 (9)</td>
<td>4.6 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td>Proximal colon (Peyer's)</td>
<td>4.5 ± 0.2 (9)</td>
<td>4.7 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>4.5 ± 0.3 (9)</td>
<td>4.5 ± 0.1 (3)</td>
<td></td>
</tr>
<tr>
<td>Tonsil</td>
<td>4.2 ± 0.4 (9)</td>
<td>5.1 ± 0.1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Category IIIa (Tissues with some infectivity)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciatic nerve</td>
<td>3.1 ± 0.3 (9)</td>
<td>3.6 ± 0.3 (3)</td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td>&lt;2.8 ± 0.3 (9)</td>
<td>4.3 ± 0.2 (3)</td>
<td></td>
</tr>
<tr>
<td>Distal colon</td>
<td>&lt;2.7 ± 0.2 (9)</td>
<td>3.3 ± 0.5 (3)</td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>&lt;</td>
<td>2.5 ± 0.2 (9)</td>
<td>4.9</td>
</tr>
<tr>
<td>nasal mucosa</td>
<td>&lt;2.3 ± 0.2 (9)</td>
<td>3.6 ± 0.2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

* All titres are expressed as log_{10} i.c. LD_{50} /g or ml of tissue
Annex 2 (contd)

a) Scapie infectivity titres in tissues from naturally infected sheep and goats with clinical disease
(continued)

<table>
<thead>
<tr>
<th>T I S S U E S</th>
<th>T I T R E S (mean ± SEM of (n) samples) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHEEP (34-57 months)</td>
</tr>
<tr>
<td>Thymus</td>
<td>&lt;2.2 ± 0.2 (9)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;2.1 ± 0.1 (9)</td>
</tr>
<tr>
<td>Lung</td>
<td>&lt;2.0 (9)</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;2.0 ± 0.1 (9)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>&lt;2.0 ± 0.1 (9)</td>
</tr>
</tbody>
</table>

Category IIIb (Tissues with minimal infectivity)

Faeces               ... <2.0 (3)
Heart                <2.0 (9) ...
Kidney               <2.0 (9) <2.0 (3)
Mammary gland        <2.0 (7) <2.0 (3)
Milk                 ... <1.0 (3)
Ovary                <2.0 (7) <2.0 (3)
Salivary glands      <2.0 (9) <2.0 (3)
Seminal vesicle      <2.0 (1) ...
Skeletal muscle      <2.0 (9) <2.0 (1)
Testis               <2.0 (1) ...
Thyroid              <2.0 (9) ...
Uterus               <2.0 (3) <2.0 (3)
Blood clot           <1.0 (9) <1.0 (3)
Serum                ... <1.0 (3)
Saliva               <1.0 (9) ...

Category IV (Tissues with no detectable infectivity)

* All titres are expressed as log_{10}i.c. LD_{50}/g or ml of tissue

NOTE: None of the Category IV tissues had any detectable infectivity. Therefore the values shown represent maxima based on the limits of the sensitivity of the bio-assay in mice.

The above is a re-analysis of the data published in refs 21 & 22.
Annex 2 (contd)

b) Scrapie infectivity titres in category I and II tissues from preclinically infected sheep compared to clinical cases

**TITRES (Mean ±SEM of (n) samples)**

<table>
<thead>
<tr>
<th>T I S S U E S</th>
<th>PRE-CLINICAL</th>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0-8 months)</td>
<td>(10-14 months)</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cerebral cortex</td>
<td>... &lt;2.0 (1)</td>
<td>4.4 ± 0.6 (9)</td>
</tr>
<tr>
<td>- diencephalon</td>
<td>... 2.2 (1)</td>
<td>6.0 ± 0.3 (8)</td>
</tr>
<tr>
<td>- midbrain</td>
<td>... &lt;2.0 (1)</td>
<td>6.1 ± 0.4 (8)</td>
</tr>
<tr>
<td>- medulla</td>
<td>... 3.8 (1)</td>
<td>5.8 ± 0.2 (8)</td>
</tr>
<tr>
<td>Cervical cord</td>
<td>... &lt;2.0 (1)</td>
<td>5.4 ± 0.3 (9)</td>
</tr>
<tr>
<td>AVERAGES</td>
<td>&lt;2.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Category I (Central nervous system - CNS)

Category II (Lymphoreticular system - LRS)

Lymph nodes
- BM           | ... <2.0 (8) | 4.1 (1) 4.5 ± 0.2 (9) |
- MP           | <2.0 (16) 3.3 ± 0.4 (8) 5.2 (1) (9) |
- PreS         | <2.0 (16) <2.0 (8) 4.5 (1) 3.7 ± 0.4 (8) |
- PreF         | <2.0 (6) <2.4 ± 0.2 (3) 3.2 (1) (9) |
- RP           | <2.0 (16) 3.8 ± 0.4 (3) 5.2 (1) (9) |
- Ileum        | <2.0 (16) <3.1 ± 0.5 (3) 5.3 (1) (9) |
- Proximal colon | ... <3.2 ± 0.5 (3) 5.1 (1) |
- Spleen       | <2.0 (16) 3.0 ± 0.4 (3) 4.3 (1) (9) |
- Tonsil       | <2.0 (10) <2.6 ± 0.3 (3) 4.7 (1) (9) |
| AVERAGES     | <2.0 < 2.8 | 4.64.3 |   |               |

* All titres are expressed as log10 i.c. LD50/g or ml of tissue.
a) None of the tissues from lambs aged 8 months or less had any detectable infectivity. The values shown represent maxima based on the limits of the sensitivity of the bio-assay in mice.

b) Infectivity was detected in only 8 out of 15 sheep exposed to scrapie.

c) Infectivity was detected in only 1 out of 3 sheep exposed to scrapie.

The above is a re-analysis of the data published in ref. 21.
### Annex 3

**SUPPORTING DOCUMENT/INTERNATIONAL ANIMAL HEALTH CODE**

**Chapter 3.2.13. Explanatory Notes**

<table>
<thead>
<tr>
<th>Article</th>
<th>Relevant paragraphs in supporting document</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1</td>
<td>11.1 ; 12</td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2.1</td>
<td>11.4.2 ; 11.4.3 ; 12.3 ; 12.4</td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2.1</td>
<td>7</td>
<td>In this context notifiable means compulsory reportable to the Veterinary Administration of the Country where the disease has occurred.</td>
</tr>
<tr>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2.1</td>
<td>7. ; 14.1 ; 14.4.4 ; 11.4.3 ; 11.5 ; 14.2 ; 12.5</td>
<td>It is acceptable to import cattle from countries with a low incidence of BSE which could have been fed on ruminant protein (e.g. before the implementation of a ruminant protein ban) because there is a negligible risk that any exported animal will be incubating disease.</td>
</tr>
</tbody>
</table>
3.2.1  3.5  et
3.2.1  3.8

14.4

a) In both the English and French texts "slaughtered" "killed" or "mis à mort" include causing death on a farm and do not restrict it to abattoirs.

b) In the context of BSE, ante mortem inspection will be an additional safeguard, aiding detection of any unexpected occurrence of BSE and because BSE cannot be detected by gross meat inspection procedures. Animals younger than six months are excluded from this requirement because there is no risk of detectable BSE occurring in this age of animal.

c) A requirement that meat comes from animals not fed ruminant-derived protein has not been included. The measures listed in 3.2.13.5. and 3.2.13.8. ensure the safety of meat whether or not an animal has been exposed to a feed source of infection by removing those tissues which might contain the BSE agent from healthy animals used for consumption.

d) re 3.2.13.8. 4)
Importing countries have two options in regard to this article. Either to import boneless meat (which will have no visible lymphatic or nervous tissue present) or to import bone-in-meat which will have had exposed lymphatic and nervous tissue (including spinal cord) removed. In the latter there may be residual lymphatic and nervous tissue that might be exposed in the country importing the carcase meat when the side or quarter of beef is further cut. This will mean that further residue of lymphatic and nervous tissue will accrue in that country. This may present no risk or an acceptable risk depending on the precise conditions under which the carcase meat is imported and the particular source and age of animal from which it is derived.
### Supporting Document/International Animal Health Code

#### Chapter 3.2.13. Explanatory Notes

<table>
<thead>
<tr>
<th>3.2.13.6 et 3.2.13.9</th>
<th>11.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.13.7</td>
<td>7</td>
</tr>
<tr>
<td>11.4.1</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

The ban referred to in paragraph 1) applies equally to other tissues, including mesenteric lymph nodes, when these are not separated from the listed tissues.

<table>
<thead>
<tr>
<th>3.2.13.10</th>
<th>3 à 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

In practice, most countries with BSE have imposed a wider ban on the feeding to ruminants (or cattle in France) of all protein derived from ruminants (except milk and milk products).

<table>
<thead>
<tr>
<th>3.2.13.11</th>
<th>3 à 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

a) In considering the origin of the animal it is important that all herds that the animal has been in are looked at since BSE has a long incubation period and is caused by exposure to infected feed.

b) Recommendations, guidelines and advice in this field issued by the World Health Organisation should be taken into consideration.
REFERENCES


15. DHSS (1984). - Management of patients with spongiform encephalopathy (Creutzfeldt-Jakob disease (CJD)). DHSS Circular DS (84) 16.


