WORKING DOCUMENT FOR THE MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY

PARIS

23-25 October 2002
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(INCLUDING AMENDMENTS TO THE SCIENTIFIC REPORT ATTACHED TO THE OPINION OF 21 JANUARY 2000)
ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE
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UPDATED OPINION ON THE SAFETY WITH REGARD TO TSE RISKS OF GELATINE DERIVED FROM RUMINANT BONES OR HIDES
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AT ITS MEETING OF 12-13 SEPTEMBER 2002
(including REPORT ON THE CURRENT STATE OF KNOWLEDGE ON THE TSE INFECTICITY CLEARANCE CAPACITY OF VARIOUS GELATINE PRODUCTION PROCESSES.
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(3) Diagnosis
- THE EVALUATION OF TESTS FOR THE DIAGNOSIS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY, 8 JULY 1999

- DESIGN OF A FIELD TRIAL FOR THE EVALUATION OF NEW RAPID BSE POST MORTEM TESTS, ADOPTED ON 22 FEBRUARY 2002

- REPORT, THE EVALUATION OF FIVE RAPID TESTS FOR THE DIAGNOSIS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY IN BOVINES (2ND STUDY), 27 MARCH 2002

(4) Report of the previous meeting of the Ad hoc group on bovine spongiform encephalopathy
1. Provisional list of participants
OIE AD HOC GROUP
ON BOVINE SPONGIFORM ENCEPHALOPATHY


MEMBERS

Dr Dagmar Heim
Co-ordination TSE
Office vétérinaire fédéral
Schwarzenburgstrasse 161
Case Postale 3003
Bern
SWITZERLAND
Tel: (41-31) 324 9993
Fax: (41-31) 323 8594
E-mail: dagmar.heim@bvet.admin.ch

Dr Stuart C. MacDiarmid
National Manager (Risk Analysis) and Adjunct Professor in Veterinary Biosecurity (Massey University)
Biosecurity Authority
Ministry of Agriculture and Forestry
P.O. Box 2526
Wellington
NEW ZEALAND
Tel: (64-4) 474 4223
Fax: (64-4) 474 4133
E-mail: macdiarmid@maf.govt.nz

Dr John A. Kellar
Disease Surveillance Science Advisory and Management Division
Canadian Food Inspection Agency
3851 Fallowfield Road
Room C305
Nepean, Ontario K1A 0Y9
CANADA
Tel: (1.613) 228 66 98
Fax: (1.613) 991 69 88 & 228 66 75
E-mail: jkellar@em.agr.ca

Dr Stuart C. MacDiarmid
National Manager (Risk Analysis) and Adjunct Professor in Veterinary Biosecurity (Massey University)
Biosecurity Authority
Ministry of Agriculture and Forestry
P.O. Box 2526
Wellington
NEW ZEALAND
Tel: (64-4) 474 4223
Fax: (64-4) 474 4133
E-mail: macdiarmid@maf.govt.nz

Dr Danny Matthews
TSE Programme Manager
Veterinary Laboratories Agency
Woodham Lane
New Haw, Addlestone
Surrey KT15 3NB
UNITED KINGDOM
Tel: (44.1932) 35 95 12
Fax: (44.1932) 35 49 29
E-mail: d.matthews@vla.maff.gsi.gov.uk

Dr Koen Van Dyck
Tel: (32-2) 298 43 34
Fax: (32-2) 296 90 62
E-mail: koen.van-dyck@ec.eu.int

Dr Maura N. Ricketts
Medical Officer APH/CSR/CDS WHO, Rm L410, Ave Appia 1211 Geneva 27 SWITZERLAND
Tel: (41) 22 791-3935
Fax: (41) 22 791 4893
E-mail: rickettsm@who.ch

Prof. Vincenzo Caporale
Director
Istituto Zooprofilattico Sperimentale dell’Abruzzo e del Molise ‘G. Caporale’
Via Campo Bosaro
64100 Teramo
ITALY
Tel: (39.0861) 33 22 33
Fax: (39.0861) 33 22 51
E-mail: caporale@izs.it

Prof. Vincenzo Caporale
Director
Istituto Zooprofilattico Sperimentale dell’Abruzzo e del Molise ‘G. Caporale’
Via Campo Bosaro
64100 Teramo
ITALY
Tel: (39.0861) 33 22 33
Fax: (39.0861) 33 22 51
E-mail: caporale@izs.it

Dr A. Thiermann
President of the OIE International Animal Health Code Commission
12 rue de Prony
75017 Pari
FRANCE
Tel.: (33.1) 44 15 18 69
Fax:(33.1) 42 67 09 87
E-mail: a.thiermann@compuserve.com

Dr. David Wilson
Head, International Trade Department
Tel.: 33 (0) 44.15.18.90
Fax: 33 (0) 42.67.09.87
E-mail: d.wilson@oie.int

OIE CENTRAL BUREAU

Dr Bernard Vallat
Director General
12 rue de Prony
75017 Paris
FRANCE
Tel: 33 - (0) 44 15 18 88
Fax: 33 - (0) 42 67 09 87
E-mail: oie@oie.int

Dr Alejandro A. Schuchel
Head, Scientific and Technical Department
Tel.: 33 (0) 44.15.18.82
Fax: 33 (0) 42.67.09.87
E-mail: a.schuchel@oie.int

Dr David Wilson
Head, International Trade Department
Tel.: 33 (0) 44.15.18.80
Fax: 33 (0) 42.67.09.87
E-mail: d.wilson@oie.int

Dr Dewan Sibartie
Deputy Head, Scientific and Technical Department
Tel.: 33 (0) 44.15.18.94
Fax: 33 (0) 42.67.09.87
E-mail: d.sibartie@oie.int

Dr Hiroyuki Kamakawa
Chargé de mission, International Trade Department
Tel.: 33 (0) 44.15.18.92
Fax: 33 (0) 42.67.09.87
E-mail: h.kamakawa@oie.int

2. Provisional Agenda
OIE AD HOC GROUP
ON BOVINE SPONGIFORM ENCEPHALOPATHY


Provisional Agenda

1. Update on significant scientific advances on BSE and its relationship with other TSE’s

2. Issues raised by countries regarding the current International Animal Health Code Chapter (2.3.13.) on BSE
   - Commodities
   - Cohorts
   - Risk Categories
   - Surveillance
   - Alternative uses of MBM


4. Issues arising from meeting of the OIE Ad hoc group on country freedom from BSE

5. Any other issues
3. Country comment received since July meeting of Code Commission on a proposed revised BSE Chapter
Country comment received since July meeting of Animal Health Code Commission. Revisions marked in chapter are as proposed by the Code Commission following its July meeting.

CHAPTER 2.3.13.

BOVINE SPONGIFORM ENCEPHALOPATHY

Article 2.3.13.1.

The recommendations in this chapter are intended to manage the human and animal health risks associated with the presence of the bovine spongiform encephalopathy (BSE) agent in cattle (Bos taurus and B. indicus) only.

Article 2.3.13.2.

The BSE status of the cattle population of a country or zone can only be determined on the basis of the following criteria:

1) the outcome of a risk assessment identifying all potential factors for BSE occurrence and their historic perspective, in particular:
   a) the potential for introduction and recycling of the BSE agent through consumption by cattle of meat-and-bone meal or greaves of ruminant origin;
   b) importation of meat-and-bone meal or greaves potentially contaminated with a transmissible spongiform encephalopathy (TSE) or feedstuffs containing either;
   c) importation of animals or embryos/oocytes potentially infected with a TSE;
   d) epidemiological situation concerning all animal TSE in the country or zone;
   e) extent of knowledge of the population structure of cattle, sheep and goats in the country or zone;
   f) the origin and use of ruminant carcasses (including fallen stock), by-products and slaughterhouse waste, the parameters of the rendering processes and the methods of animal feed manufacture;

2) on-going awareness programme for veterinarians, farmers, and workers involved in transportation, marketing and slaughter of cattle to encourage reporting of all cases of neurological disease in adult cattle;

3) compulsory notification and investigation of all cattle showing clinical signs compatible with BSE;

4) a BSE surveillance and monitoring system with emphasis on risks identified in point 1) above, taking into account the guidelines in Appendix 3.8.4.; records of the number and results of investigations should be maintained for at least 7 years;

5) examination in an approved laboratory of brain or other tissues collected within the framework of the aforementioned surveillance system.

Standards for diagnostic tests are described in the Manual.
Appendix VI (contd)

BSE free country or zone

The cattle population of a country or zone may be considered free of BSE should the following conditions be met:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) either:

   a) there has been no case of BSE; and either:

      i) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years; or

      ii) the criteria in point 3) of Article 2.3.13.2. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

   OR

   b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:

      i) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years; or

      ii) the criteria in point 3) of Article 2.3.13.2. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

   OR

   c) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years and the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced for at least 8 years.

Article 2.3.13.4.

BSE provisionally free country or zone

The cattle population of a country or zone may be considered as provisionally free of BSE should the following conditions be met:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;
2) either:

a) there has been no case of BSE; and either:

i) the criteria in points 2) to 5) of Article 2.3.13.2. are complied with, but have not been complied with for 7 years; or

ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.2. have not been complied with for 7 years;

OR

b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:

i) the criteria in points 2) to 5) of Article 2.3.13.2. are complied with, but have not been complied with for 7 years; or

ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.2. have not been complied with for 7 years.

Article 2.3.13.5.

Country or zone with a minimal BSE risk

The cattle population of country or zone may be considered as presenting a minimal BSE risk should the country or zone comply with the following requirements:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) EITHER:

a) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.2. are complied with and the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants is effectively enforced, but:

i) the criteria in points 2) to 5) of Article 2.3.13.2. have not been complied with for 7 years; or

ii) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has not been effectively enforced for 8 years;
Appendix VI (contd)

OR

b) the last indigenous case of BSE has been reported less than 7 years ago, and the BSE incidence rate, calculated on the basis of indigenous cases, has been less than one case per million during each of the last four consecutive 12-month periods within the cattle population over 24 months of age in the country or zone (Note: For countries with a population of less than one million adult cattle, the maximum allowed incidence should be expressed in cattle-years), and:

i) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced for at least 8 years;

ii) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years;

iii) the affected cattle as well as:

- if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,

- all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.6.

Country or zone with a moderate BSE risk

The cattle population of a country or zone may be considered as presenting a moderate BSE risk if:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted, and the other criteria listed in Article 2.3.13.2. are complied with;

2) the BSE incidence rate, calculated over the past 12 months, has been:

a) greater than, or equal to, one indigenous case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

b) less than one indigenous case per million for less than four consecutive 12-month periods (Note: For countries with a population of less than one million adult cattle, the maximum allowed incidence should be expressed in cattle-years);

3) the affected cattle as well as:

a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed.

Countries and zones where the BSE incidence rate has been less than one indigenous case per million within the cattle population over 24 months of age during each of the last four consecutive 12-month periods, but where at least one of the other requirements to be considered as provisionally free from BSE or as presenting a minimal BSE risk is not complied with, shall be considered as countries or zones with a moderate BSE risk.

**Article 2.3.13.7.**

**Country or zone with a high BSE risk**

The cattle population of a country or zone may be considered as presenting a high BSE risk if:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted, the other criteria listed in Article 2.3.13.2. are complied with, and the BSE incidence rate, calculated over the past 12 months, has been greater than one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

2) the BSE incidence rate, calculated over the past 12 months, has been greater than, or equal to, one case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone, but at least one of the other requirements to be considered as presenting a moderate BSE risk is not complied with.

**Article 2.3.13.8.**

Regardless of the BSE status of the exporting country, Veterinary Administrations should authorise without restriction the import or transit through their territory of the following commodities:

1) milk and milk products;

2) semen and embryos;

3) protein-free tallow (maximum level of insoluble impurities of 0.15% in weight) and derivatives made from this tallow;

4) dicalcium phosphate (with no trace of protein or fat);

5) hides and skins;

6) gelatin and collagen prepared exclusively from hides and skins.
Appendix VI (contd)

Article 2.3.13.9.

When importing from a BSE free country or zone, *Veterinary Administrations* should require:

for all *commodities* from cattle not listed in Article 2.3.13.8,

the presentation of an *international veterinary certificate* attesting that the country or zone complies with the conditions in Article 2.3.13.3. to be considered as free of BSE.

Article 2.3.13.10.

When importing from a BSE provisionally free country or zone, *Veterinary Administrations* should require:

for *cattle*

the presentation of an *international veterinary certificate* attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.4. to be considered as provisionally free of BSE;

2) cattle selected for export are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect females.

Article 2.3.13.11.

When importing from a country or zone with a minimal BSE risk, *Veterinary Administrations* should require:

for *cattle*

the presentation of an *international veterinary certificate* attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be considered as presenting a minimal BSE risk;

2) the feeding of ruminants with *meat-and-bone meal* and greaves derived from ruminants has been banned and the ban has been effectively enforced;

**New Comment**

**New Zealand**

*It is a matter of opinion as to what constitutes "effective" enforcement of any ban.*

3) cattle selected for export:
   
a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females;

b) were born after the date from which the ban on the feeding of ruminants with *meat-and-bone meal* and greaves derived from ruminants has been effectively enforced.
Article 2.3.13.12.
When importing from a country or zone with a moderate BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be considered as presenting a moderate BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) cattle selected for export:
   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females;
   b) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced.

Article 2.3.13.13.

When importing from a country or zone with a high BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.7. to be considered as presenting a high BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) the affected cattle as well as:
   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
   b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed;
Appendix VI (contd)

4) cattle selected for export:
   a) are identified by a permanent identification system enabling them to be traced back to the dam
      and herd of origin and are not the progeny of BSE suspect or confirmed females;
   b) were born at least 2 years after the date from which the ban on the feeding of ruminants with
      meat-and-bone meal and greaves derived from ruminants was effectively enforced.

   Article 2.3.13.14.

When importing from a BSE provisionally free country or zone, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.4. to be considered as provisionally
   free of BSE;
2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for
   export originate.

   Article 2.3.13.15.

When importing from a country or zone with a minimal BSE risk, Veterinary Administrations should
require:

for fresh meat (bone-in or deboned) and meat products from cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be considered as presenting a
   minimal BSE risk;
2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for
   export originate;
3) cattle from which the meat or meat products destined for export originate were not subjected to a
   stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial
   cavity or to a pithing process (laceration, after stunning, of central nervous tissue by means of an
   elongated rod-shaped instrument introduced into the cranial cavity);
4) the fresh meat and meat products destined for export [have neither been contaminated by, nor do not
   contain [either] brain, eyes, spinal cord or mechanically separated meat from skull and vertebral column from
   cattle over 30 months of age, all of which have been removed in a hygienic manner.

New Comment

New Zealand

Articles 2.3.13.15, 2.3.13.16, 2.3.13.17. Not only is it a matter of opinion as to what constitutes "hygienic"
removal of the listed tissues, the level of hygiene has no influence on the BSE risk, so should not be mentioned.
Sanitary measures prescribed in any Article in the International Animal Health Code should be specific to the
disease under consideration in the particular Chapter.
Article 2.3.13.16.

When importing from a country or zone with a moderate BSE risk, *Veterinary Administrations* should require:

*for fresh meat (bone-in or deboned) and meat products from cattle*

the presentation of an *international veterinary certificate* attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be considered as presenting a moderate BSE risk;

2) the feeding of ruminants with *meat-and-bone meal* and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) ante-mortem inspection is carried out on all bovines;

4) cattle from which the meat or *meat products* destined for export originate were not subjected to a stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial cavity or to a pithing process;

5) the *fresh meat* and *meat products* destined for export [have neither been contaminated by, nor do not contain brain, eyes, spinal cord, distal ileum or mechanically separated meat from skull and vertebral column from cattle over 6 months of age, all of which have been removed in a hygienic manner.]

Article 2.3.13.17.

When importing from a country or zone with a high BSE risk, *Veterinary Administrations* should require:

*for fresh meat and meat products from cattle*

the presentation of an *international veterinary certificate* attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.7. to be considered as presenting a high BSE risk;

2) the meat destined for export [if obtained from animals over 9 months of age, has been deboned and have neither been contaminated by, nor contains] does not contain the tissues listed in point 1) of Article 2.3.13.19. [nor nervous and lymphatic tissues exposed during a deboning process], all of which have been removed in a hygienic manner;

3) the meat destined for export, if obtained from animals over 9 months of age, has been deboned and does not contain nervous and lymphatic tissues exposed during a deboning process, all of which have been removed in a hygienic manner;

4) the *meat products* destined for export are derived from deboned meat and [have neither been contaminated by, nor do not contain the tissues listed in point 1) of Article 2.3.13.19. nor nervous and lymphatic tissues exposed during a deboning process, nor mechanically separated meat from skull and vertebral column of bovine animals, all of which have been removed in a hygienic manner;
Appendix VI (contd)

5) a system is in operation enabling the fresh meat and meat products destined for export to be traced back to the establishments from which they are derived;

6) ante-mortem inspection is carried out on all bovines;

7) the cattle from which the meat or meat products destined for export originate:
   a) were identified by a permanent identification system enabling them to be traced back to the dam and herd of origin;
   b) are not the progeny of BSE suspect or confirmed females; and either:
      i) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced; or
      ii) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years;
   c) were not subjected to a stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial cavity or to a pithing process;

8) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

9) the affected cattle as well as:
   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
   b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

   if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.18.

Ruminant-derived meat-and-bone meal or greaves, or any commodities containing such products, which originate from countries with a minimal, moderate or high BSE risk should not be traded between countries.
New Comment

New Zealand

Although this Article is not marked for revision with either double underlines or [square brackets and small font], we respectfully suggest that, for consistency with the layout of other articles (e.g. Article 2.3.13.9), the article needs to be rewritten to start with the risk and move to commodity.

1) The following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices: brains, eyes, spinal cord, tonsils, thymus, spleen, intestines, dorsal root ganglia, trigeminal ganglia, skull and vertebral column, and protein products derived therefrom, from cattle over 6 months of age originating from countries with a high BSE risk. Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using these commodities should also not be traded.

2) The following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices:
   a) brains, eyes, spinal cord, distal ileum, skull, vertebral column and protein products derived therefrom, from cattle, originating from a country or zone with a moderate BSE risk, that were at the time of slaughter aged over 6 months;
   b) brains, eyes and spinal cord, skull, vertebral column and protein products derived therefrom, from cattle, originating from a country or zone with a minimal BSE risk has been reported, that were at the time of slaughter aged over 30 months.

Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using the commodities listed in points a) and b) above should also not be traded.

New Comment

New Zealand

Similarly, although this Article is not marked for revision either, our experts in the Food Safety Authority consider that there is a need for Code to make it clear whether the words “food, feed, fertilisers, cosmetics…” in this Article are limited to, or extend beyond, the protection of animal health.

Veterinary Administrations of importing countries should require:

for gelatin and collagen prepared from bones and intended for food or feed, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that the bones came from:

1) a BSE free or provisionally free country or zone, or from a country or zone with a minimal BSE risk; or
Appendix VI (contd)

2) a country or zone with a moderate BSE risk; and
   a) skulls and vertebrae (excluding tail vertebrae) have been excluded;
   b) the bones have been subjected to a process which includes all the following steps:
      i) pressure washing (degreasing),
      ii) acid demineralisation,
      iii) prolonged alkaline treatment,
      iv) filtration,
      v) sterilisation at ≥138°C for a minimum of 4 seconds,

or to an equivalent process in terms of infectivity reduction.

   Article 2.3.13.21.

Veterinary Administrations of importing countries should require:

for tallow (other than protein-free tallow as defined in Article 2.3.13.8.) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that it originates from:

1) a BSE free or provisionally free country or zone; or

2) a country or zone with a minimal BSE risk, and
   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)b) of Article 2.3.13.19.;
   b) if prepared by rendering, (under study); or

3) a country or zone with a moderate BSE risk; and
   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)a) of Article 2.3.13.19.;
   b) if prepared by defatting of bones:
      i) skulls and vertebral columns from cattle over 6 months of age have been excluded; or
      ii) it has been processed using a method that reduces the infectivity by at least $5 \log_{10} \text{LD}_{50}/\text{g}$ (processes under study);
Appendix VI (contd)

c) if prepared by rendering, (under study).

Article 2.3.13.22.

Veterinary Administrations of importing countries should require:

for tallow derivatives (other than those made from protein-free tallow as defined in Article 2.3.13.8.)
intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that:

1) they originate from a BSE free or provisionally free country or zone, or from a country or zone with
   a minimal BSE risk;

OR

2) they have been produced by hydrolysis, saponification or transesterification using high temperature
   and pressure.

Article 2.3.13.23.

Careful selection of source materials is the best way to ensure maximum safety of ingredients or reagents
of bovine origin used in the manufacture of medicinal products.

Countries wishing to import bovine materials for such purposes should therefore consider the following
factors:

1) the BSE status of the country and herd(s) where the animals have been kept, as determined under the
   provisions of Articles 2.3.13.2. to 2.3.13.7.;

2) the age of the donor animals;

3) the tissues required and whether or not they will be pooled samples or derived from a single animal.

Additional factors may be considered in assessing the risk from BSE, including:

4) precautions to avoid contamination during collection of tissues;

5) the process to which the material will be subjected during manufacture;

6) the amount of material to be administered;

7) the route of administration.

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[ ] deleted
4. Issues raised by Member Countries regarding Current Code chapter on BSE
Issues raised regarding the current Code chapter on BSE

This paper summarises the issues raised regarding the current Code chapter on BSE before, during and after the General Session, and which have not yet been addressed by the Code Commission.

The Code chapter on BSE adopted at the 71st General Session is attached for reference.

Commodities

Comment has been received querying the safety of:

- tallow – the EU has indicated that it would provide information at a later date regarding manufacturing processes (such as rendering and defatting of bones) which may inactivate the agent
- dicalcium phosphate – due to doubts as to whether the commercially-prepared end product could be free from protein or fat - the June 1998 Opinion of the EU SSC is attached
- certain raw materials, including skulls, used for gelatin manufacture; the EU Scientific Steering Committee (EU SSC) is examining the issue - the April 1998 Opinion of the EU SSC is attached.

By what process could tallow be prepared which would allow it to be safely traded?

By what process could gelatin be prepared from bones which would allow it to be safely traded?

Comment has been received on the risks presented by commodities such as fresh meat, meat products and intestines, and the appropriate age group restrictions needed to address the risks:

- for a country or zone with a moderate BSE risk: a suggestion has been received that no meat or meat product should contain skull, brain, eyes, tonsils or spinal cord from bovine animals over 12 months, intestine from bovine animals of any age, nor mechanically separated meat from the skull or vertebral column; this suggestion is based on the January 1998 Opinion of the EU SSC that an extremely cautious limit for the CNS as a highly infective tissue could be set at 12 months and provide considerable reassurance of non-infectivity, and that limiting the use of CNS to less than 6 months might only be necessary if animals are derived from high risk areas
- for a country or zone with a moderate BSE risk: a suggestion has been received that the Opinion of the EU SSC of November 2000 (attached) be followed in that the intestine of bovine animals of all ages should be removed whenever it is not highly unlikely that the slaughtered animals are infected
- for a country or zone with a high BSE risk: for meat and meat products, the suggestions are that
  a. meat from animals over 9 months of age should be deboned and, no matter the age of the animal, meat products should only be derived from deboned meat
b. no matter the age of the animal, meat and meat products should not contain commodities listed in point 1 of Article 2.3.13.19, nor nervous nor lymphatic tissue exposed during a deboning process.

there was a suggestion that, as the commodities listed in Article 2.3.13.19 are likely to contain the BSE agent, they should not be traded, no matter the BSE risk category (minimal, moderate, high) of the exporting country.

**Taking into account the current approach in the BSE chapter to trade in commodities which are likely to be contaminated with the BSE agent**

- for countries or zones in the moderate risk category, what are the age restrictions which should be imposed on commodities such as fresh meat, meat products, intestines and mechanically separated meat which would allow them to be safely traded?

- for countries or zones in the high risk category, what are the age restrictions which should be imposed on fresh meat and meat products which would allow them to be safely traded?

**Cohorts**

The current chapter requirements for the treatment of birth cohorts are ambiguous and need to be updated.

**What risks are presented by the progeny of BSE-affected female cattle, born one year or two years prior to the onset of clinical signs?**

**Risk categories**

Comment has been received on the current ‘cut-off’ points for the three BSE risk categories (minimal, moderate and high), regarding the need to take account of active surveillance systems and the additional positive results being generated in countries using such systems. The current cut-off points are arbitrary, are based on the original diagnostic methods for BSE and on passive surveillance systems, and do not reflect the current approach of many countries. These cut-off points are:

- for a country or zone with a minimal BSE risk: less than 1 indigenous case per million
- for a country or zone with a moderate BSE risk: between 1 and 100 indigenous cases per million
- for a country or zone with a high BSE risk: either more than 100 indigenous cases per million, or between 1 and 100 indigenous cases per million if one of the other requirements for moderate BSE risk status has not been complied with

Suggestions received from Member Countries include:

- ‘based on a statistically valid active monitoring programme, the BSE incidence rate has been …
for a country or zone with a minimal BSE risk: less than 2 indigenous cases per million

for a country or zone with a moderate BSE risk: either between 2 and 200 indigenous cases per million, or between 2 and 100 indigenous cases per million from active surveillance and between 2 and 100 indigenous cases per million from passive surveillance (proposed additional wording)

for a country or zone with a high BSE risk: either more than 200 indigenous cases per million, or between 2 and 200 indigenous cases per million but one of the other requirements for moderate BSE risk status has not been complied with

The November 2001 Opinion of the EU SSC (attached) on requirements for statistically authoritative BSE/TSE surveys is relevant.

- in Article 2.3.13.6 (which deals with countries or zones with a moderate BSE risk), additional words has been proposed as follows:

‘Countries and zones where the BSE incidence rate has been less than one indigenous case per million within the cattle population over 24 months of age during each of the last four consecutive 12-month periods, but where at least one of the other requirements to be considered as provisionally free from BSE or as presenting a minimal BSE risk is not complied with, shall be considered as countries or zones with a moderate BSE risk, unless the results of a statistically valid active surveillance system provide sufficient additional evidence of absence of the disease.

What modifications to the BSE chapter, if any, should be made to these cut-off points to address active surveillance systems?

Surveillance

Countries have requested that improved guidance regarding rapid testing and sample sizes be incorporated into Appendix 3.6.4. Ideally, this Appendix should contain recommendations for sampling each of the three sub-populations (animals displaying clinical signs, fallen stock and cattle subject to emergency slaughter, and cattle subject to normal slaughter) according to the type of testing employed. It should also contain a description of a methodology for combining the results obtained from each sub-population to meet the surveillance and monitoring obligations of Member Countries.

The November 2001 Opinion of the EU SSC (attached) on requirements for statistically authoritative BSE/TSE surveys is relevant here.

What changes should be made to Appendix 3.6.4 to better incorporate the new rapid tests and give improved guidance re sampling each of the three sub-populations?

What methodology could be used to combine the results obtained from all three sub-populations to meet the BSE surveillance and monitoring obligations of Member Countries?
**Alternative uses of MBM**

Several Member Countries have asked about the safety of using MBM in cement and for power production.

The current Code chapter recommends against trading in ruminant MBM or greaves from countries not free or provisionally-free from BSE. This restriction was based on the assumption that the material would be used for a ‘biological’ purpose.

**What recommendations could be made about the use of ruminant derived MBM for the production of cement and in power plants?**
5. Issues raised by the recent meetings of OIE Standards Commission
(1) Proposed revised OIE Manual
- revisions proposed by the Standards Commission

(Chapter 2.3.13. – Bovine spongiform encephalopathy)
CHAPTER 2.3.13.

BOVINE SPONGIFORM ENCEPHALOPATHY

SUMMARY

Bovine spongiform encephalopathy (BSE) is a fatal neurological disease of adult cattle that was first recognised in Great Britain (GB) in 1986. The pathological changes, the epidemiological pattern, and the transmissibility of the disease indicate that BSE is one of the spongiform encephalopathies caused by unconventional transmissible agents or prions. The archetype for this group of diseases is scrapie of sheep and goats (see Chapter X.9. Scrapie).

The current epizootic of BSE can be explained by oral exposure to a scrapie-like agent in the ruminant-derived protein of meat-and-bone meal included in proprietary concentrates or feed supplements. Initial cases of BSE in some other countries are considered to be the result of exports from GB of infected cattle or contaminated meat-and-bone meal, although exportations from other countries are now implicated. In others, initial cases are clearly indigenous, with no clear link with imported meat-and-bone meal, suggesting that earlier, undetected, cases may have occurred. A ban on the feeding of ruminant-derived protein to ruminants was first implemented in GB in July 1988. Since then, the feeding of mammalian-derived protein to ruminants has, with certain exemptions, been prohibited throughout the European Union and some other countries. From April 1996, this ban, with respect to mammalian meat-and-bone meal, was extended in the United Kingdom (UK) to all farmed food animals. Commission Decision 2000/766/EC of December 2000, included a temporary ban on the feeding of processed animal proteins to farmed animals kept for the production of food. Experimental transmissibility of BSE to cattle has been demonstrated following parenteral and oral exposure to brain tissue from affected cattle. Epidemiological studies in GB have revealed an increased risk for the offspring of clinical cases of BSE developing the disease themselves, but this enhanced risk will not maintain endemic infection in the national cattle population. As a result of control measures the epizootics in the UK, Portugal and Switzerland are in decline. Cases of BSE currently occur throughout most of Europe and have now also been detected in Asia.

The BSE agent is believed also to be the common source of transmissible spongiform encephalopathies (TSEs) in several other species of bovidae and in species of felidae. There is evidence of a causal link between the BSE agent and a new variant form of the human TSE, Creutzfeldt-Jakob disease (CJD).

BSE, as it occurs in GB, has a peak incidence in cattle aged between 4 and 5 years. The clinical course is variable but can extend to several months. Overt clinical signs are sufficiently distinctive to lead to suspicion of disease, particularly if differential diagnoses are eliminated. Early clinical signs may be subtle, and may lead to disposal of affected animals before suspicion of BSE is triggered. In countries with a statutory policy toward the disease, clinically suspect cases must be slaughtered, the brain examined and affected cattle destroyed. Confirmation of the diagnosis is based primarily on histopathological examination of the brain. Lesions have been described only in the central nervous system (CNS). Recommendations for safety precautions for handling BSE-infected material now assume that BSE is a zoonosis and a containment category 3 (with derogation) has been ascribed.

Identification of the agent: No diagnostic test for the BSE agent in the live animal is presently available. The nature of the agents causing the TSE is unresolved. A disease-specific partially protease-resistant isoform of a membrane protein PrP\(^{1}\) (PrP\(^{\text{res}}\)) has a critical importance in the

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\(^{1}\) PrP: Prion protein
To confirm the diagnosis of spongiform encephalopathy, histological examination of the brain is necessary. The correlation between the clinical diagnosis and the neurohistological diagnosis in BSE can, with appropriate experience, be greater than 90%. The histopathological examination may also provide a differential diagnosis in clinically suspect cases in which lesions of BSE are not detected. The pathognomonic lesion is spongiform change in grey matter neuropil and neuronal vacuolation of certain brainstem nuclei. This change is usually, but not invariably, bilaterally symmetrical. Detection of accumulations of abnormal PrP (PrPres) in the CNS of affected cattle by immunohistochemical methods offers a disease-specific diagnostic approach. PrPres can be detected in unfixed brain extracts by immunoblotting and other enzyme immunoassay methods. Characteristic patterns of accumulations of disease-specific PrP in formalin-fixed affected brain can be demonstrated by immunohistochemical methods. Both approaches are now widely used as confirmatory diagnostic methods. Characteristic fibrils, homologous with scrapie-associated fibrils and composed of PrPres, can be visualised by electron microscopic examination of detergent-treated extracts of unfixed (or formalin-fixed) BSE-affected brains and have also been used to confirm the diagnosis, but lack the diagnostic performance of the standard immunohistochemical methods.

BSE can be transmitted from brain tissue of terminally affected cattle to mice by intracerebral/intraperitoneal inoculation or by feeding, but incubation periods of several months precludes bioassay from routine use. This is the only practical method currently available for detection of infectivity.

Serological tests: Specific immune responses have not been detected in scrapie or other TSEs.

Requirements for vaccines and diagnostic biologicals: There are no biological products available currently.

A. INTRODUCTION

A detailed account of bovine spongiform encephalopathy (BSE), its experimental transmissibility (20, 25), occurrence, epidemiology, clinical signs, pathology, diagnosis, prevention, and control has been given previously in English, French and Spanish (39). More recent reviews have provided updated information (16, 17, 45). BSE is an invariably fatal disease of domestic cattle, cases of which were first recognised in Great Britain (GB) in November 1986 (72). BSE has been shown to belong to that group of disorders known as the transmissible spongiform encephalopathies (TSE) or prion diseases, typified in animal species by scrapie of sheep. These diseases are defined by the pathological accumulation, principally in the central nervous system (CNS) but also in lymphoreticular and peripheral nervous tissues, of an abnormal partially protease-resistant isoform of a host-encoded protein, designated PrPres. Retrospective studies have indicated that the first cases of BSE presented around April 1985. The initial epidemiological studies established that the occurrence of BSE was in the form of an extended common source epizootic, due to feedborne infection with a scrapie-like agent in meat-and-bone meal used as a dietary protein supplement.

BSE has occurred in several countries other than the United Kingdom (UK) involving imported and/or indigenous cattle. The origin of such cases is most likely to have resulted directly or indirectly from the export of infected cattle or infected meat-and-bone meal from countries with occurrences of BSE, including historically the UK. It is probable that infection has subsequently been propagated within countries in which cases have occurred. Indeed, in some countries, the only cases detected reflect indigenous exposure rather than direct linkage with imported contaminated feed. Cases of BSE within indigenous cattle populations outside the UK have now been recorded in most European countries where efficient surveillance or monitoring systems have been applied. These include Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Liechtenstein, Luxembourg, the Netherlands, Portugal, Spain, Switzerland, the Czech Republic, Slovakia, Slovenia, Austria, Greece, Israel and Poland. In addition BSE has been identified in Japan. For current statistics on BSE around the world, readers should refer to the OIE Web site.

From July 1988 in GB and from January 1989 in Northern Ireland, the feeding of ruminant-derived protein to ruminants was prohibited. With some exceptions, a ban on the feeding of mammalian-derived protein to ruminant animals has since been introduced elsewhere; in Switzerland (December 1990) (66) and throughout the European Union (June 1994) (45). From April 1996, this ban, at least when protein is presented in the form of
meat-and-bone meal, was extended in the UK to all farmed food animals, including horses and fish. From 1 January 2001 the use of mammalian meat-and-bone meal and fishmeal was prohibited.

Experimentally it has been demonstrated that BSE can be transmitted to cattle following parenteral and oral exposure to brain tissue from affected cattle (20, 70). Epidemiological studies in Britain have revealed an increased risk for the offspring of clinical cases of BSE developing the disease themselves (77). Whether or not this is due to true maternal transmission has not been established. It is considered that this enhanced risk will not maintain endemic infection in the national (UK) cattle population. There is no evidence of horizontal transmission of BSE between cattle. Epidemiological and transmission studies have not revealed evidence of a risk from semen (79) or milk (42, 64) or through embryos (79). As a result of control measures, the epizootics in the UK and Switzerland (32) are in decline, others are showing the early effects of controls in the form of changes in age-specific incidence. In some countries the controls have not been in place long enough for the effects to be recognised. Interpretation of the status of epidemics in Europe has been enhanced by the introduction of active surveillance using rapid diagnostic tests, identifying infected animals that have not progressed to clinical onset.

The novel occurrence of TSE in several species of captive exotic bovidae and felidae and in domestic cats, during the course of the BSE episode is suspected, or, in specific instances, known to have been caused by the BSE agent. Exposure is presumed to have been via feed.

In the past epidemiological studies have found no connection between the exposure of humans to agents causing animal spongiform encephalopathies and the occurrence of the human TSE Creutzfeldt-Jakob disease (CJD). In particular no enhanced occupational or dietary risk from exposure to sheep products has been established, thus suggesting that scrapie agents are not a human health hazard under natural conditions of exposure. However, monitoring of cases of CJD in the UK resulted, in March 1996, in the announcement of the recognition of ten cases of an apparently new variant of sporadic CJD (v-CJD) in the UK (78). As of January 2001, 104 cases of v-CJD have been reported in the UK. Four cases have been reported in France (14), and another in Ireland, while one patient recognised in Hong Kong is considered to have been exposed during a period of residence in the UK.

Strain-typing studies of the causal agent of v-CJD in mice (10, 58) have provided strong evidence that the same strain of agent derived from BSE is also found in v-CJD. Studies showing similarities between the Western blot banding and glycosylation patterns of the disease-related isoform of PrPres from patients with v-CJD and from certain animal species with naturally acquired or experimentally transmitted BSE, also support this conclusion (18, 33). Therefore, on present evidence, the most likely explanation of cases of v-CJD is exposure to the BSE agent. The current incidence of the disease must still be viewed with caution. It is therefore now recommended that safety precautions for handling the BSE agent be based on the assumption that BSE is transmissible to humans. Containment category 3 (with derogation) has been assigned (47). Because the incubation period of v-CJD is unknown, it is too early to predict the course of the epidemic. Attempts to do so have produced widely varying predictions, although as cases continue to appear the confidence limits are narrowing (19, 26–28, 35, 45).

BSE affects adult cattle from approximately 2 years of age, but most cases occur in animals 4–5 years of age. There is no breed predilection, but the incidence of affected herds by functional type is much greater for dairy than beef, as, in the UK, it was mainly calves from dairy herds that were fed on concentrate rations containing meat-and-bone meal. Onset of clinical signs is not associated with season or stage of breeding cycle.

BSE has an insidious onset and usually a slowly progressive course (8, 39, 72, 76). Rarely, a case will present with acute signs and then deteriorate rapidly (76). Presenting signs, though variable, usually include behavioural changes, apprehension, and hyper-reactivity. For example, affected cows may be reluctant to enter the milking parlour or may kick vigorously during milking. In dry cows especially, pelvic limb incoordination and weakness can be the first clinical features to be noticed. Neurological signs predominate throughout the clinical course and may include many aspects of altered mental status and behaviour, abnormalities of posture and movement, and aberrant sensation, but the most commonly reported nervous signs are apprehension, pelvic limb ataxia, and hyperaesthesia to touch and sound. The intense pruritus characteristic of some sheep with scrapie is not prominent in cattle with BSE, though in a proportion of cases there is rubbing and scratching activity. Affected cows will sometimes stand with low head carriage, the neck extended and the ears directed caudally (67).

Abnormalities of gait include swaying of the pelvic quarters and pelvic limb hypermetria; features that are most readily appreciated when cattle are observed at pasture. Gait ataxia may also involve the pectoral limbs and, with advancing severity of locomotor signs, generalised weakness, resulting in falling and recumbency, can dominate the clinical picture. Reports of reduced ruminination (2, 4), also bradycardia and altered heart rhythm (3), though not specific signs, suggest that autonomic disturbance is a feature of BSE. General clinical features of loss of bodily condition, decreasing live weight, and reduction in milk yield often accompany nervous signs as the disease progresses. There has been no change in the clinical picture of BSE over the course of the epizootic in the UK (75). Clinical signs are essentially similar in other countries where BSE has occurred (8). The protracted clinical course, extending usually over a period of weeks or months, would eventually require slaughter on welfare considerations. However, a statutory policy to determine the BSE status of a country requires compulsory notification and diagnostic investigation of clinically suspect cases, their slaughter and the complete destruction of the carcasses of affected cattle (46). Early in the disease course, the signs may be subtle, variable and nonspecific, and thus may prevent clinical diagnosis on an initial examination. Continued observation of such
equivocal cases, together with appropriate clinical pathology procedures to eliminate differential diagnoses, especially metabolic disorders, will establish the essential progression of signs. Some early clinical signs of BSE may show similarities with features of nervous ketosis, hypomagnesaemia, encephalic listeriosis and other encephalitides. Subtle signs may sometimes be exacerbated following stress, such as that caused by transport. Because of the link established between BSE and v-CJD, BSE and related TSE agents are now categorised, in respect to biohazard, with the human TSE (1). Consequently, veterinarians and laboratory workers conducting necropsies on BSE-suspect animals or handling tissues derived from such animals, must conduct the work under appropriate containment conditions (category 3) (47), sometimes with derogations allowed by the nature of the work and the results of local risk assessment. It is important that appropriate protective clothing be worn and that a strict code of practice be followed to prevent exposure to the agent. Laboratories conducting work on BSE must comply with national biocontainment and biosafety regulations. Recommended decontamination procedures may not be completely effective when dealing with high-titre material or when the agent is protected within dried organic matter. Recommended physical inactivation is by porous load autoclaving at 134°C–138°C for 18 minutes at 30 lb/in². However, temperatures at the higher end of the range may be less effective than those at the lower end and total inactivation may not be achieved under certain conditions, such as when the test material is in the form of a macerate (62). Disinfection is carried out using sodium hypochlorite containing 2% available chlorine, or 2 N sodium hydroxide, applied for more than 1 hour at 20°C for surfaces, or overnight for equipment (63).

B. DIAGNOSTIC TECHNIQUES

1. Identification of the agent

The nature of the agents causing animal or human TSEs remains unresolved (53). The disease-specific modified form (PrPres) of a host-coded, highly conserved, membrane protein (PrPC) of unknown function, is the only disease-specific macromolecule identified in the scrapie-like diseases. A substantial scientific view is that the agent is composed entirely of the disease-specific isoform of PrP and that the altered form is capable of inducing conversion of the normal form: the protein only or ‘prion’ hypothesis. The opposing view is that the agent is a virus or is virus-like and contains nucleic acid. The identification of multiple ‘strains’ or isolates of scrapie agents, with characteristic incubation periods and patterns of neuropathological change when transmitted to mice, is considered to be more in keeping with this latter hypothesis. Previous studies to determine the resistance of the agent to degeneration have been used to suggest that the TSE agents do not contain nucleic acids. However, recent critical analyses of the denaturation characteristics of TSE agents, including effects of ultraviolet and ionising irradiation, extremes of temperatures, autoclaving and a large range of chemical disinfectants, suggest that the data obtained are compatible with that obtained for small viruses (15). The molecular basis for strain variation is still unclear, although proponents of the prion hypothesis argue that it is not incompatible with the existence of distinct strains (49).

Characterisation of isolates by transmission of BSE to mice has shown that BSE is caused by a single major strain of agent that differs from characterised strains of the scrapie agent in sheep (9). Uniformity of the pathology among affected cattle has also supported the notion of a single BSE strain and enabled the definition of a particular disease phenotype for BSE (71). This specific pattern of neuropathology in the host species is an important feature of the case definition of BSE. In the absence of in-vitro methods for isolation of the causative agent, the conventional basis of confirmation of the diagnosis in this group of diseases has been the demonstration of the morphological features of spongiform encephalopathy by histopathological examination. This remains necessarily, by definition, the only method by which this characteristic vacuolar pathology can be diagnosed. However, given the essential role of the PrPres molecule and increases in technical capabilities in this area, it is now important that diagnostic approaches use one or more methods for the detection of the abnormal form of the protein. The demonstration by electron microscopy on CNS extracts of characteristic fibrils, termed scrapie-associated fibrils (SAF), which are composed largely of PrPres, is a further morphological diagnostic method. Methods of disease-specific PrP detection include immunohistochemical demonstration, Western blotting and, most recently, a number of other rapid immunoassays for screening. The use of a particular method will depend on the purpose to which the diagnosis is to be applied in the epidemiological context. This range of purposes will extend from confirmation of the clinical diagnosis in the control of epizootic disease to the screening of healthy populations for evidence of covert or preclinical disease. The pathological case definition adopted will also differ according to whether the method is to be applied for confirmation of a case or for screening of a population. For the former it is important to use approaches that can monitor the pathological phenotype of BSE. It is also clear that the performance of individual methods will be crucial to this process of selection of a single method or a portfolio approach. It must be stressed that the development of methods, particularly rapid screening immunoassays for the detection of PrPres, is a rapidly evolving field.

The initial pathological case definition of BSE was based on the histopathological changes in the CNS, and this has provided the usual basis for confirmation of the clinical diagnosis of BSE (68, 72). The histopathological examination also allows confirmation of the characteristic neuropathological phenotype of BSE (60, 74). The histopathological changes are neurodegenerative and closely resemble those of scrapie in sheep. The most prominent features are vacuolar and comprise a spongiform change in the neuropil of grey matter and single or multiple vacuoles within neuronal perikarya. The precise appearance of the spongiform change in TSEs, as observed by light microscopy, has been defined previously (40). In BSE, spongiform change is the predominant...
form of vacuolar change. Both forms of vacuolation are bilaterally distributed and usually symmetrical with a consistent pattern of severity relative to distribution throughout the brain (69, 74). The high frequency of occurrence of neuroparenchymal vacuolation in certain anatomic nuclei of the medulla oblongata at the level of the obex has, in the BSE epizootic in the UK, provided a satisfactory means of establishing a diagnosis on a single section of the medulla (68). However, observation of doubtful lesions in the medulla at this level requires examination of other brain areas to detect cases of BSE with minimal or potentially atypical lesions and, when necessary, to establish pathological differential diagnoses. Neurodegenerative changes other than vacuolation are not prominent in BSE. A gliosis (astrocytosis), as seen in scrapie, is another feature, particularly in sites of vacuolar change. Detection of gliosis is assisted by the use of special stains and immuno-histochemistry. For example, astrocytosis can be demonstrated by the immunohistochemical detection of increased glial fibrillary acidic protein (GFAP).

For the preparation of material for diagnostic examination, cattle suspected of having the disease should be killed with an intravenous injection of a concentrated barbiturate solution following sedation, if necessary. The technical procedures concerned with collection, fixation, and histological processing have been described (7, 55) and are revised and summarised below.

In all circumstances of surveillance of neurological disease in adult cattle where the occurrence of BSE within a country or state has not been established or is of low incidence, it is important that a standard neuropathological approach be followed in which representative areas of the whole brain are examined. Departure from this is dependent on local national circumstances, including whether or not a differential diagnosis is required.

Brain tissue should be removed as soon as possible after death. Fresh material for potential use in tests to detect disease-specific PrP should be taken ideally as a complete coronal section (2–4 g) from the medulla, caudal to the obex, specifically avoiding damage to the obex region. The cervical spinal cord and the lateral hemisphere of cerebellum also offer optimal sampling areas that will not encroach on histopathological requirements. This tissue is stored frozen prior to testing. If the remaining whole brain is sampled for the histopathological examination, it should be placed in approximately 4–6 litres of 10% formol saline fixative, which should be changed twice weekly. After fixation for 2 weeks, the brain is cut into coronal slices. The fixation time may be shortened by cutting the fresh brain stem into smaller coronal pieces, leaving intact the diagnostically important areas at the obex, the cerebellar peduncles and the rostral colliculi. Depending on some other factors (temperature, agitation, use of microwave) the fixation time for these small pieces of brainstem may be reduced to 2–5 days. The other formol-fixed parts of the brain may be used for differential diagnosis after completing the standard 2 weeks’ fixation.

Initially, a single block cut at the obex of the medulla oblongata (Figure 1) should be selected for histological processing by conventional paraffin wax embedding methods for neural tissue. Sections, cut at 5 µm thickness and stained with haematoxylin and eosin, are examined for characteristic spongiform change and neuronal vacuolation. If results are inconclusive because of minimal lesions, or the material is histologically uninterpretable due to autolysis or damage, it is necessary to carry out additional tests, including immunohistochemistry (IHC) or immunoblotting.

![Brainstem after the removal of the cerebellum, from a) dorsal, and b) lateral aspects. Recommended levels at which sections should be taken: A-A = medulla, at the obex; B(B = medulla through caudal cerebellar peduncles; C(C = midbrain through rostral](image-url)
When the occurrence of BSE in a particular country has been established in the indigenous cattle population, and there is evidence that the distribution of lesions is consistent with that seen in the brains of cattle from the UK epizootic, it is adequate for monitoring purposes to remove the hind brain alone (Figure 1). This can be achieved via the foramen magnum without removal of the calvarium. This will reduce the amount of fixative required, thereby lowering costs and improving safety, while maintaining representation of the major target areas for histological examination. The diagnosis may be confirmed if completely typical changes are present in the medulla (obex) section. When lesions are not obvious in the medulla (obex), sections of other parts of the brainstem (Figure 1) should be examined. However, given the constant lesion pattern, this is unlikely to contribute additional confirmation in more than 0.5% of cases of BSE where lesions are absent in the medulla (obex) section (68). Clearly this abridged protocol does not allow a full neuropathological examination for differential diagnoses to be established.

The interpretation of observed vacuolar changes in the bovine brain must be approached with caution. Vacuoles within the perikarya, indistinguishable from those of BSE, have been reported in neurons of the red and oculomotor nuclei of the midbrain and other brainstem nuclei as an incidental finding in cattle (23, 41, 72). Thus, like the diagnosis of scrapie, which may be confounded by the occurrence of such neuronal vacuolation scattered in the medullae of healthy sheep (see Chapter X.9. Scrapie) (66, 67), histopathological diagnosis of BSE must not rely on the presence of occasional solitary vacuolated neurons. Even relatively numerous vacuolated neurons in the red nucleus and in the habenular nuclei must be disregarded. The presence of spongiform change in specific neuroanatomical locations in BSE provides the most confidence of minimising false-positive diagnoses.

As with scrapie of sheep, the possibility of BSE cases occurring in which brain lesions are minimal or undetectable by light microscopy, is a potential problem that can be resolved only by diagnostic criteria independent of histopathology (55, 73). (See also below.)

For routine diagnosis in countries with a high incidence of BSE, histopathological examination confined to the medulla oblongata is the laboratory investigational method used to handle the large number of suspect cases. Demonstration of typical changes provides a definitive diagnosis. Where the result of the histopathological examination is inconclusive or negative or the brain material taken post-mortem was unsuitable for the histological examination because of autolysis or damage, it is important that the disease-specific diagnostic criterion of the detection of abnormal accumulation of PrP be applied. It is also increasingly important to apply such tests in the decaying phase of epizootic occurrence and in surveillance programmes where the most critical monitoring of disease is required. Individual National authorities should apply the use of additional laboratory diagnostic methods such as immunoblotting, IHC or the detection of SAF where their use is considered to be appropriate.

In conjunction with, or even as an alternative to, the histopathological evaluation of medulla sections is the use of IHC to detect PrPSc accumulation in formalin-fixed, paraffin-embedded material (31, 74). Several different protocols have been applied successfully to the IHC detection of PrP for the diagnosis of BSE (29, 31, 38, 74). Harmonisation toward a fully validated standardised routine diagnostic IHC method is desirable. However, it is likely that only the general principles can be prescribed, with precise methods being determined by each individual laboratory. The technique is more sensitive than routine histopathology as it can detect cases in the last months of incubation before the occurrence of vacuolar changes, at least in experimentally induced cases of BSE (45) and possibly also in the natural disease (22). BSE can therefore be diagnosed by IHC in animals with equivocal morphological changes. The technique does not require lengthy tissue fixation and, providing the tissue can be adequately processed histologically, the technique works well in autolysed tissues in which morphological evaluation is no longer possible. IHC detection of abnormal PrP accumulations is as sensitive as the Western blotting method for detection of PrPres (52). In combination with good histological preparations, IHC allows detection of abnormal PrP accumulations and, as this abnormal PrP accumulation, like the vacuolar pathology, exhibits a typical distribution pattern and appearance, it provides simultaneous evaluation or confirmation of the disease phenotype. In countries with low BSE incidence, IHC is therefore a method of choice for both confirmatory diagnosis and surveillance.

Abnormal accumulations of PrP as shown by IHC are considered to have potential for the preclinical diagnosis of scrapie in sheep using tonsillar (54) or nictitating membrane (48) lymphoid tissue biopsies. Failure to detect infectivity in lymphoid tissues, other than in distal ileum containing Peyer’s patches of experimentally infected cattle, at any time throughout the incubation period and clinical disease course by mouse bioassay (70) and by IHC, suggests that these approaches are currently unlikely to be of use diagnostically in BSE.

Detection of PrPres by electrophoretic separation and immunoblotting techniques (24, 34, 61), is carried out on fresh (unfixed) or frozen brain or spinal cord material. Improvements in purification methods for extracting PrP (6, 21) have contributed to increased sensitivity of this method. Automated Western blot and enzyme-linked immunosorbent assay (ELISA) techniques have been developed allowing screening of large numbers of brain samples (44, 52). Such techniques can be performed rapidly and are potentially more sensitive than the histopathological evaluation. In a European Commission trial (44), it was demonstrated that one such Western immunoblot method, or either of two specific ELISA methods, when evaluated on brain tissue, were suitable for diagnostic use in specifically targeted populations. This evaluation was restricted to a comparison of the
examination of a sample of brains of cattle identified as suspect clinical animals with histopathological changes characteristic of BSE and a sample of brains of cattle from New Zealand that were unexposed to BSE and histopathologically negative. These tests are now approved and used in European and some other countries for large-scale screening and surveillance programmes. They provide a means of initial screening for animals in the late stages (the last few months) of the incubation period, for example in surveys of post-mortem material collected from routinely slaughtered cattle. In countries conducting surveillance for the detection of the novel occurrence of BSE and in those countries in which a means, independent of the system of notification of suspect cases, of assessing the prevalence of BSE is considered necessary, these recently developed screening tests offer an efficient approach. Since their introduction for active screening in Europe from January 2001, such tests have been responsible for the identification of the majority of BSE-infected animals. In some countries, given the speed with which results can be obtained, the rapid tests are the preferred primary test, but confirmation of a diagnosis of BSE requires examination of fixed brain by histopathology and/or immunocytochemistry.

The processing of the brain tissue for use in the rapid test should be carried out precisely as specified by the supplier or manufacturer of the test method or kit. Details of this procedure vary from method to method and should not be changed without supportive validation data for the variant methodology. The preferred sample for immunoassay should be at, or within, 1.5 cm anterior to the obex. Because of the uneven distribution of PrPSC, sample size should be as specified in the diagnostic kit or if not specified should be at least 0.5 g. Performance characteristics of all of the tests may be compromised by autolytic changes. In order to reduce hazard to the operators collecting large numbers of samples for an active surveillance programme, bovine brains should be sampled without opening the cranium. This is readily achieved, even at abattoirs, following training of operators in the use of a specially designed spoon, which can be inserted through the foramen magnum of the severed head. The following is a protocol that has been drafted by the OIE Reference Laboratory, Bern, Switzerland.

- Removal of the brainstem

After the head has been separated from the body between the atlas and foramen magnum, the head is put on a support with the frontal bone down; the caudal end of the brain stem is visible through the foramen magnum. The brainstem is dissected through the foramen magnum without opening the skull by means of a ‘teaspoon’ with sharp edges and a long handle (Fig. 2). The spoon is inserted into the foramen magnum between the brainstem and the bone and moved along the wall of the skull moving to the left and the right to sever the cranial nerves on both sides, while avoiding damage to the brain tissue by keeping close to the bone. The spoon is advanced for a distance of approximately 7 cm in this fashion and then bent downwards cutting and separating the caudal medulla oblongata (with some fragments of cerebellum) from the rest of the brain. The spoon – remaining in a bent downward position – is then pulled towards the operator. In this way the severed brainstem slips out of the skull through the foramen magnum.

Fig. 2. The head is separated from the body and placed on a support upside down; the brainstem (bs) is separated from the bone with cutting movements left and right (curved arrows) by means of a long-handled ‘teaspoon’ with sharp edges, inserted in the foramen magnum between bone and brain tissue. The preferred sample for immunoassay should be at, or within 1.5 cm anterior to the obex.
A further generation of rapid diagnostic tests was evaluated by the European Commission in 2001. The process has highlighted the need for such an evaluation process, and identified the dangers of using research tools prematurely for active surveillance. Although the evaluation programme is in support of European legislation on surveillance for BSE, the consequences are of relevance to other countries as well. The consequences of false-positive or false-negative results are so great that the introduction of new tests should be supported by thorough evaluation of test performance. Claims by test manufacturers should always be supported by data, ideally evaluated independently. It must be stressed that the process of full validation of all of these diagnostic methods for BSE has been restrained by the lack of a true gold standard and the consequent need to apply standards of comparison based on relatively small studies. There is therefore a continuing need for the publication of larger scale studies of assay performance, and none of the data published so far equate with recognised procedures for test validation for other diseases. The consequences of false-positive or false-negative results are so great that the introduction of new tests should be supported by thorough evaluation of test performance. Claim s by test manufacturers should always be supported by data, ideally evaluated independently. It must be stressed that the process of full validation of all of these diagnostic methods for BSE has been restrained by the lack of a true gold standard and the consequent need to apply standards of comparison based on relatively small studies. There is therefore a continuing need for the publication of larger scale studies of assay performance, and none of the data published so far equate with recognised procedures for test validation for other diseases. The studies initiated by the European Commission represent evaluations of the tests: test validation is currently ongoing. Caution must be exercised in the comparative interpretation of tests applied to apparently healthy animals as different tests may vary in their sensitivities relative to stage of incubation and pathogenesis of the disease.

The demonstration of characteristic fibrils, the bovine counterpart of SAF (see Chapter X.9. Scrapie), by negative-stain electron microscopy in detergent extracts of fresh or frozen brain or spinal cord tissue (57, 61, 72) has been used as an additional diagnostic method for BSE and may be particularly useful when histopathological approaches are precluded by the occurrence of post-mortem decomposition (56). Recent work on scrapie indicates that, with modification, the method may be applied successfully to formalin-fixed tissue (12). Detection of fibrils has been shown to correlate well with the histopathological diagnosis of BSE (59), but does not offer the specificity or sensitivity available from IHC or immunoblotting methods. Some of the rapid immunological tests are also effective in the presence of autolysis (13) and given their greater sensitivity than SAF detection, may be the preferred tests in such circumstances.

Quality control (QC) and quality assessment (QA) should form an essential part of the testing procedures. The OIE Reference Laboratories can be contacted to provide assistance in this area and to help develop interlaboratory comparisons at the international level.

BSE infection can be shown by intracerebral/intraperitoneal inoculation (25) or by feeding mice with brain tissue from terminally affected cattle (5), but bioassay is impractical for routine diagnosis because of the long incubation period ((292 days). Further development of transgenic mice over expressing the bovine PrP gene may potentially offer bioassays with reduced incubation periods for BSE. However, data obtained from one such study did not derive incubation periods substantially shorter than that of conventional mouse strains (11).

2. Serological tests

Similarities with scrapie, in which no immune response in the host has been detected, suggest that there is not likely to be an immune response in BSE.

3. Other tests

There remains the need for a test for BSE that can be applied to the live animal and has a sensitivity capable of detecting PrP res at the low levels, such as may occur in the early stages of incubation of the disease. Potential routes of diagnosis are published from time to time, often of a preliminary nature and based on limited amounts of data. None has progressed to the point of peer review and evaluation by others, and claims should be interpreted with care.

Certain protein markers, notably apolipoprotein E (Apo E), can be detected by two-dimensional gel electrophoresis in cerebrospinal fluid of clinically suspected, histopathologically confirmed cases of BSE (37). Apo E is, however, a nonspecific marker for neurodegeneration and has not been shown to be useful for diagnosis of preclinical cases of BSE. Assay of cerebrospinal fluid for the 14-3-3 protein is not of diagnostic use in BSE (51). Similarly, studies of S-100 proteins in cerebrospinal fluid (30) and serum (50) did not give results that would provide diagnostically useful tests for BSE. The electrochemical detection of metabolites in urine (36) has a final performance validation that gave specificity and sensitivity values below that required for it to have a possible independent role in the diagnosis of BSE. Preliminary data indicating that a derivative of the PrP molecule may be detected in the urine of infected cattle (59) is leading to further investigations with a view to the marketing of a diagnostic test kit, but further evaluation and peer review of the data are required.
C. REQUIREMENTS FOR VACCINES AND DIAGNOSTIC BIOLOGICALS

There are no biological products available currently.

REFERENCES


*   *
*   *
(2) Letter from Prof. Martin H. Groschup
(to be provided at meeting)
6. Background Material
(1) BSE Chapter and Surveillance and monitoring systems for bovine spongiform encephalopathy (as adopted at 2002 General Session)
CHAPTER 2.3.13.

BOVINE SPONGIFORM ENCEPHALOPATHY

Article 2.3.13.1.

The recommendations in this chapter are intended to manage the human and animal health risks associated with the presence of the bovine spongiform encephalopathy (BSE) agent in cattle (Bos taurus and B. indicus) only.

Article 2.3.13.2.

The BSE status of the cattle population of a country or zone can only be determined on the basis of the following criteria:

1) the outcome of a risk assessment identifying all potential factors for BSE occurrence and their historic perspective, in particular:
   a) the potential for introduction and recycling of the BSE agent through consumption by cattle of meat-and-bone meal or greaves of ruminant origin;
   b) importation of meat-and-bone meal or greaves potentially contaminated with a transmissible spongiform encephalopathy (TSE) or feedstuffs containing either;
   c) importation of animals or embryos/oocytes potentially infected with a TSE;
   d) epidemiological situation concerning all animal TSE in the country or zone;
   e) extent of knowledge of the population structure of cattle, sheep and goats in the country or zone;
   f) the origin and use of ruminant carcasses (including fallen stock), by-products and slaughterhouse waste, the parameters of the rendering processes and the methods of animal feed manufacture;

2) on-going awareness programme for veterinarians, farmers, and workers involved in transportation, marketing and slaughter of cattle to encourage reporting of all cases of neurological disease in adult cattle;

3) compulsory notification and investigation of all cattle showing clinical signs compatible with BSE;

4) a BSE surveillance and monitoring system with emphasis on risks identified in point 1) above, taking into account the guidelines in Appendix 3.8.4.; records of the number and results of investigations should be maintained for at least 7 years;

5) examination in an approved laboratory of brain or other tissues collected within the framework of the aforementioned surveillance system.

Standards for diagnostic tests are described in the Manual.

Article 2.3.13.3.

BSE free country or zone

The cattle population of a country or zone may be considered free of BSE should the following conditions be met:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) either:
   a) there has been no case of BSE; and either:
i) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years; or

ii) the criteria in point 3) of Article 2.3.13.2. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

OR

b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:

i) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years; or

ii) the criteria in point 3) of Article 2.3.13.2. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

OR

c) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years and the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced for at least 8 years.

Article 2.3.13.4.

BSE provisionally free country or zone

The cattle population of a country or zone may be considered as provisionally free of BSE should the following conditions be met:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) either:

a) there has been no case of BSE; and either:

i) the criteria in points 2) to 5) of Article 2.3.13.2. are complied with, but have not been complied with for 7 years; or

ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.2. have not been complied with for 7 years;

OR

b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:

i) the criteria in points 2) to 5) of Article 2.3.13.2. are complied with, but have not been complied with for 7 years; or

ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.2. have not been complied with for 7 years.
Article 2.3.13.5.

**Country or zone with a minimal BSE risk**

The cattle population of country or zone may be considered as presenting a minimal BSE risk should the country or zone comply with the following requirements:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) EITHER:

   a) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.2. are complied with and the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants is effectively enforced, but:

      i) the criteria in points 2) to 5) of Article 2.3.13.2. have not been complied with for 7 years; or

      ii) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has not been effectively enforced for 8 years;

   OR

   b) the last indigenous case of BSE has been reported less than 7 years ago, and the BSE incidence rate, calculated on the basis of indigenous cases, has been less than one case per million during each of the last four consecutive 12-month periods within the cattle population over 24 months of age in the country or zone (Note: For countries with a population of less than one million adult cattle, the maximum allowed incidence should be expressed in cattle-years.), and:

      i) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced for at least 8 years;

      ii) the criteria in points 2) to 5) of Article 2.3.13.2. have been complied with for at least 7 years;

      iii) the affected cattle as well as:

         - if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,

         - all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

         if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.6.

**Country or zone with a moderate BSE risk**

The cattle population of a country or zone may be considered as presenting a moderate BSE risk if:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted, and the other criteria listed in Article 2.3.13.2. are complied with;

2) the BSE incidence rate, calculated over the past 12 months, has been:

   a) greater than, or equal to, one indigenous case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

   b) less than one indigenous case per million for less than four consecutive 12-month periods (Note: For countries with a population of less than one million adult cattle, the maximum allowed incidence should be expressed in cattle-years.);

3) the affected cattle as well as:

   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life, if alive in the country or zone, are slaughtered and completely destroyed.

Countries and zones where the BSE incidence rate has been less than one indigenous case per million within the cattle population over 24 months of age during each of the last four consecutive 12-month periods, but where at least one of the other requirements to be considered as provisionally free from BSE or as presenting a minimal BSE risk is not complied with, shall be considered as countries or zones with a moderate BSE risk.

**Article 2.3.13.7.**

**Country or zone with a high BSE risk**

The cattle population of a country or zone may be considered as presenting a high BSE risk if:

1) a risk assessment, as described in point 1) of Article 2.3.13.2., has been conducted, the other criteria listed in Article 2.3.13.2. are complied with, and the BSE incidence rate, calculated over the past 12 months, has been greater than one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

2) the BSE incidence rate, calculated over the past 12 months, has been greater than, or equal to, one case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone, but at least one of the other requirements to be considered as presenting a moderate BSE risk is not complied with.

**Article 2.3.13.8.**

Regardless of the BSE status of the exporting country, Veterinary Administrations should authorise without restriction the import or transit through their territory of the following commodities:

1) milk and milk products;
2) semen and embryos;
3) protein-free tallow (maximum level of insoluble impurities of 0.15% in weight) and derivatives made from this tallow;
4) dicalcium phosphate (with no trace of protein or fat);
5) hides and skins;
6) gelatin and collagen prepared exclusively from hides and skins.

**Article 2.3.13.9.**

When importing from a BSE free country or zone, Veterinary Administrations should require:

for all commodities from cattle not listed in Article 2.3.13.8.

the presentation of an international veterinary certificate attesting that the country or zone complies with the conditions in Article 2.3.13.3. to be considered as free of BSE.

**Article 2.3.13.10.**

When importing from a BSE provisionally free country or zone, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.4. to be considered as provisionally free of BSE;
2) Cattle selected for export are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect females.

Article 2.3.13.11.

When importing from a country or zone with a minimal BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be considered as presenting a minimal BSE risk;

2) cattle selected for export:

   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females;

   b) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced.

Article 2.3.13.12.

When importing from a country or zone with a moderate BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be considered as presenting a moderate BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) cattle selected for export:

   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females;

   b) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced.

Article 2.3.13.13.

When importing from a country or zone with a high BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.7. to be considered as presenting a high BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) the affected cattle as well as:

   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,

   b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected...
cattle consumed during the first year of their life,
if alive in the country or zone, are slaughtered and completely destroyed;

4) cattle selected for export:
   a) are identified by a permanent identification system enabling them to be traced back to the dam
      and herd of origin and are not the progeny of BSE suspect or confirmed females;
   b) were born at least 2 years after the date from which the ban on the feeding of ruminants with
      meat-and-bone meal and greaves derived from ruminants was effectively enforced.

   Article 2.3.13.14.

When importing from a BSE provisionally free country or zone, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.4. to be considered as provisionally
   free of BSE;
2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for
   export originate.

   Article 2.3.13.15.

When importing from a country or zone with a minimal BSE risk, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be considered as presenting a
   minimal BSE risk;
2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for
   export originate;
3) cattle from which the meat or meat products destined for export originate were not subjected to a
   stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial
   cavity or to a pithing process (laceration, after stunning, of central nervous tissue by means of an
   elongated rod-shaped instrument introduced into the cranial cavity);
4) the fresh meat and meat products destined for export have neither been contaminated by, nor contain
   either brain, eyes, spinal cord or mechanically separated meat from skull and vertebral column from
   cattle over 30 months of age.

   Article 2.3.13.16.

When importing from a country or zone with a moderate BSE risk, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be considered as presenting a
   moderate BSE risk;
2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been

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banned and the ban has been effectively enforced;

3) ante-mortem inspection is carried out on all bovines;

4) cattle from which the meat or meat products destined for export originate were not subjected to a stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial cavity or to a pithing process;

5) the fresh meat and meat products destined for export have neither been contaminated by, nor contain, brain, eyes, spinal cord, distal ileum or mechanically separated meat from skull and vertebral column from cattle over 6 months of age.

Article 2.3.13.17.

When importing from a country or zone with a high BSE risk, Veterinary Administrations should require:

for fresh meat and meat products from cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.7. to be considered as presenting a high BSE risk;

2) the meat destined for export, if obtained from animals over 9 months of age, has been deboned and has neither been contaminated by, nor contains the tissues listed in point 1) of Article 2.3.13.19. nor nervous and lymphatic tissues exposed during a deboning process;

3) the meat products destined for export are derived from deboned meat and have neither been contaminated by, nor contain the tissues listed in point 1) of Article 2.3.13.19. nor nervous and lymphatic tissues exposed during a deboning process, nor mechanically separated meat from skull and vertebral column of bovine animals;

4) a system is in operation enabling the fresh meat and meat products destined for export to be traced back to the establishments from which they are derived;

5) ante-mortem inspection is carried out on all bovines;

6) the cattle from which the meat or meat products destined for export originate:

   a) were identified by a permanent identification system enabling them to be traced back to the dam and herd of origin;
   
   b) are not the progeny of BSE suspect or confirmed females; and either:

      i) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced; or
      
      ii) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years;
   
   c) were not subjected to a stunning process, prior to slaughter, with a device injecting compressed air or gas into the cranial cavity or to a pithing process;

7) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

8) the affected cattle as well as:

   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease;
   
   b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,
if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.18.

Ruminant-derived meat-and-bone meal or greaves, or any commodities containing such products, which originate from countries with a minimal, moderate or high BSE risk should not be traded between countries.

Article 2.3.13.19.

1) The following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices: brains, eyes, spinal cord, tonsils, thymus, spleen, intestines, dorsal root ganglia, trigeminal ganglia, skull and vertebral column, and protein products derived therefrom, from cattle over 6 months of age originating from countries with a high BSE risk. Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using these commodities should also not be traded.

2) The following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices:

a) brains, eyes, spinal cord, distal ileum, skull, vertebral column and protein products derived therefrom, from cattle, originating from a country or zone with a moderate BSE risk, that were at the time of slaughter aged over 6 months;

b) brains, eyes and spinal cord, skull, vertebral column and protein products derived therefrom, from cattle, originating from a country or zone with a minimal BSE risk that has been reported, that were at the time of slaughter aged over 30 months.

Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using the commodities listed in points a) and b) above should also not be traded.

Article 2.3.13.20.

Veterinary Administrations of importing countries should require:

for gelatin and collagen prepared from bones and intended for food or feed, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that the bones came from:

1) a BSE free or provisionally free country or zone, or from a country or zone with a minimal BSE risk; or

2) a country or zone with a moderate BSE risk; and

a) skulls and vertebrae (excluding tail vertebrae) have been excluded;

b) the bones have been subjected to a process which includes all the following steps:

i) pressure washing (degreasing),

ii) acid demineralisation,

iii) prolonged alkaline treatment,

iv) filtration,

v) sterilisation at $\geq 138^\circ\text{C}$ for a minimum of 4 seconds,

or to an equivalent process in terms of infectivity reduction.
Article 2.3.13.21.

Veterinary Administrations of importing countries should require:

for tallow (other than protein-free tallow as defined in Article 2.3.13.8.) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that it originates from:

1) a BSE free or provisionally free country or zone; or
2) a country or zone with a minimal BSE risk, and
   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)(b) of Article 2.3.13.19.;
   b) if prepared by rendering, (under study); or
3) a country or zone with a moderate BSE risk; and
   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)(a) of Article 2.3.13.19.;
   b) if prepared by defatting of bones:
      i) skulls and vertebral columns from cattle over 6 months of age have been excluded; or
      ii) it has been processed using a method that reduces the infectivity by at least 5 log\textsubscript{10} LD\textsubscript{50}/g (processes under study);
   c) if prepared by rendering, (under study).

Article 2.3.13.22.

Veterinary Administrations of importing countries should require:

for tallow derivatives (other than those made from protein-free tallow as defined in Article 2.3.13.8.) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

the presentation of an international veterinary certificate attesting that:

1) they originate from a BSE free or provisionally free country or zone, or from a country or zone with a minimal BSE risk; OR

2) they have been produced by hydrolysis, saponification or transesterification using high temperature and pressure.

Article 2.3.13.23.

Careful selection of source materials is the best way to ensure maximum safety of ingredients or reagents of bovine origin used in the manufacture of medicinal products.

Countries wishing to import bovine materials for such purposes should therefore consider the following factors:

1) the BSE status of the country and herd(s) where the animals have been kept, as determined under the provisions of Articles 2.3.13.2. to 2.3.13.7.;

2) the age of the donor animals;
3) the tissues required and whether or not they will be pooled samples or derived from a single animal.

Additional factors may be considered in assessing the risk from BSE, including:

4) precautions to avoid contamination during collection of tissues;

5) the process to which the material will be subjected during manufacture;

6) the amount of material to be administered;

7) the route of administration.
APPENDIX 3.8.4.

SURVEILLANCE AND MONITORING SYSTEMS FOR BOVINE SPONGIFORM ENCEPHALOPATHY

Article 3.8.4.1.

Introduction

The surveillance strategy applied for bovine spongiform encephalopathy (BSE) should be determined by, and commensurate with the outcome of the risk assessment referred to in Article 2.3.13.2. Surveillance and risk assessment are part of an iterative process and inform each other.

Surveillance for BSE has at least two goals: one is to determine whether BSE is present in the country, and the other, once the disease has been detected, is to monitor the evolution of the epizootic, direct control measures and monitor their effectiveness.

A surveillance strategy may need to combine several methods of investigation.

Surveillance for BSE requires laboratory examination of samples in accordance with the methods described in the Manual.

For surveillance purposes, testing a part of the population is consistent with Chapter 1.3.6. on surveillance and monitoring of animal health. Recommended strategies for selecting the part of the population for testing are described below.

Article 3.8.4.2.

Examination of cattle displaying clinical signs compatible with BSE

Cattle affected by illnesses that are refractory to treatment, and displaying progressive behavioural changes such as excitability, persistent kicking when milked, changes in herd hierarchical status, hesitation at doors, gates and barriers, as well as those displaying progressive neurological signs without signs of infectious illness are candidates for examination. Since BSE causes no pathognomonic clinical signs, all countries with cattle populations will observe individual animals with compatible clinical signs. Surveillance should primarily focus on cattle over 30 months of age, but younger cattle should not be ignored.

Table 1 indicates the minimum number of clinical cases that should be subjected to diagnostic tests according to the total cattle population over 30 months of age. As this sampling is not random, the numbers indicated in this table are a subjective interpretation rather than a strict statistical deduction.
Article 3.8.4.3.

Examination of targeted cattle not displaying clinical signs compatible with BSE

Cattle that have died or have been killed for reasons other than routine slaughter (including ‘fallen’ stock and emergency slaughter) should be examined. Surveillance needs to focus on animals over 30 months of age.

Table 1. Minimum number of annual investigations of animals showing clinical signs compatible with BSE required for effective surveillance according to the total cattle population over 30 months of age

<table>
<thead>
<tr>
<th>Total cattle population over 30 months of age</th>
<th>Minimum number of samples to examine</th>
</tr>
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<tr>
<td>500,000</td>
<td>50</td>
</tr>
<tr>
<td>700,000</td>
<td>69</td>
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<tr>
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<tr>
<td>30,000,000</td>
<td>425</td>
</tr>
<tr>
<td>40,000,000</td>
<td>433</td>
</tr>
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</table>

Article 3.8.4.4.

Examination of cattle subject to normal slaughter

In countries not free from BSE, sampling at routine slaughter is a means of monitoring the progress of the epizootic and the efficacy of control measures applied, because it offers continuous access to a cattle population of known class, age structure and geographical origin.

Exclusive dependence on random sampling from normal cattle is not recommended, unless the number of samples examined annually is statistically sufficient to detect a disease prevalence of 1 in 1,000,000.

Article 3.8.4.5.

Within each of the above sub-populations, countries may wish to target cattle identifiable as imported from countries or zones not free from BSE, cattle which have consumed potentially contaminated feedstuffs from countries or zones not free from BSE, offspring of BSE affected cows and cattle which have consumed feedstuffs potentially contaminated with other TSE agents.
(2) Commodities

1. Tallow

OPINION ON QUANTITATIVE RISK ASSESSMENT ON THE USE OF THE VERTEBRAL COLUMN FOR THE PRODUCTION OF GELATINE AND TALLOW.
ADOPTED BY
THE SCIENTIFIC STEERING COMMITTEE
AT ITS MEETING OF 13-14 APRIL 2000

REVISED OPINION AND REPORT ON:
THE SAFETY OF TALLOW OBTAINED FROM RUMINANT SLAUGHTER BY-PRODUCTS
ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE AT ITS MEETING OF 28-29 JUNE 2001
(http://europa.eu.int/comm/food/fs/ssc/out219_en.pdf)

2. Dicalcium phosphate

THE SAFETY OF DICALCIUM PHOSPHATE PRECIPITATED FROM RUMINANT BONES AND USED AS AN ANIMAL FEED ADDITIVE
Report and opinion adopted at the meeting of the Scientific Steering Committee of 25-26 June 1998,
Following a public consultation on the preliminary opinion adopted on 14-15 May 1998
(http://europa.eu.int/comm/food/fs/ssc/out20_en.pdf)

OPINION AND REPORT on
THE SAFETY OF DICALCIUM PHOSPHATE PRECIPITATED FROM RUMINANT BONES AND USED AS ANIMAL FEED ADDITIVE
(Report updated at the SSC meeting of 26-27 October 2000)
(http://europa.eu.int/comm/food/fs/ssc/out146_en.pdf)

3. Gelatine

OPINION ON THE SAFETY OF GELATINE
Adopted at the Scientific Steering Committee at its plenary meeting of 26-27 March 1998
Following a public consultation on the preliminary opinion adopted on 19-20 February 1998
(Version updated on 3.04.98:
see double underlined sections in Chapters 5.4.3 and 8)
(http://europa.eu.int/comm/food/fs/ssc/out09_en.pdf)

SCIENTIFIC REPORT AND OPINION ON THE SAFETY OF GELATINE
UPDATED BY
THE SCIENTIFIC STEERING COMMITTEE
AT ITS MEETING OF 20-21 JANUARY 2000
(The corresponding sections are underlined with dots)
(http://europa.eu.int/comm/food/fs/ssc/out34_en.pdf)
UPDATED OPINION ON
THE SAFETY WITH REGARD TO TSE RISKS OF
GELATINE DERIVED FROM RUMINANT BONES OR
HIDES FROM CATTLE, SHEEP OR GOATS
(INCLUDING AMENDMENTS TO THE SCIENTIFIC REPORT ATTACHED TO
THE OPINION OF 21 JANUARY 2000)
ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE
AT ITS MEETING OF 28-29 JUNE 2001
(http://europa.eu.int/comm/food/fs/sc/ssc/out227_en.pdf)

UPDATED OPINION ON THE SAFETY WITH REGARD TO TSE RISKS OF GELATINE
DERIVED FROM RUMINANT BONES OR HIDES
ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE
AT ITS MEETING OF 12-13 SEPTEMBER 2002
(including REPORT ON THE CURRENT STATE OF KNOWLEDGE ON THE TSE
INFECTICITY CLEARANCE CAPACITY OF VARIOUS GELATINE
PRODUCTION PROCESSES.
FINALISED BY THE TSE/BSE AD HOC GROUP
AT ITS MEETING OF 5 SEPTEMBER 2002)
(http://europa.eu.int/comm/food/fs/sc/ssc/out279_en.pdf)
(3) Diagnosis

- THE EVALUATION OF TESTS FOR THE DIAGNOSIS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY, 8 JULY 1999
  (http://europa.eu.int/comm/food/fs/bse/bse12_en.pdf)

- DESIGN OF A FIELD TRIAL FOR THE EVALUATION OF NEW RAPID BSE POST MORTEM TESTS, ADOPTED ON 22 FEBRUARY 2002
  (http://europa.eu.int/comm/food/fs/sc/ssc/out246_en.pdf)

- REPORT, THE EVALUATION OF FIVE RAPID TESTS FOR THE DIAGNOSIS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY IN BOVINES (2ND STUDY), 27 MARCH 2002
  (http://europa.eu.int/comm/food/fs/bse/bse42_en.pdf)
(4) REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY (Paris, 10-12 September 2001)
REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY

Paris, 10-12 September 2001

The OIE Ad hoc Group on bovine spongiform encephalopathy met at the OIE Headquarters from 10 to 12 September 2001.

The members of the OIE Ad hoc Group and other participants are listed in Appendix I. The Agenda adopted is given in Appendix II. Dr S. MacDiarmid was appointed chairman of the Ad hoc Group.

Dr B. Vallat, Director General of the OIE, reminded the participants of the Resolution adopted by the International Committee during the 69th General Session (May 2001) requesting that the terms used in the chapter of the International Animal Health Code (the Code) on bovine spongiform encephalopathy (BSE) relating to the status of countries be amended to take into account both the incidence of the disease and the risk factors identified in the risk assessment required under Article 2.3.13.1. of the said chapter. He also underlined the need to update, on a continuous basis, the appendix of this chapter relating to surveillance, and invited the participants to reflect on a broad outline for a draft Code chapter on BSE in small ruminants. In conclusion, he thanked the participants for their support for the OIE and wished them every success with the meeting.

Dr A. Thiermann, President of the International Animal Health Code Commission, gave a summary of previous discussions on the chapter within the International Committee, and noted that certain Member Countries had indicated their wish to see the category of "BSE provisionally free country or zone where at least one indigenous case has been reported" deleted. In view of the importance that this category presents for countries where eradication of the disease is at an advanced stage, the International Animal Health Code Commission considered that this category should be retained but that its name and those of the other categories be changed to place greater emphasis on the notion of risk.

Following a discussion, the Ad hoc Group decided to analyse the contents of each article of the Code chapter on BSE to determine its purpose (management of the animal health risk at the domestic level, at the international level – management of the risk to public health at the domestic level, at the international level), so as to clearly place the question of risk in context and to shift the emphasis of the document more towards the question of public health risks in the food chain.

A study of Article 2.3.13.1. led to the conclusion that an appendix to this article was necessary to provide guidelines on how to conduct the risk analysis and study the other criteria listed in this article for a given country. Since these guidelines could not be drafted during the meeting, one of the members of the Ad hoc Group offered to prepare a preliminary draft for discussion via electronic channels with the other members of the Ad hoc Group and several other experts.

The Ad hoc Group then turned its attention to the most appropriate terms to denote each category of BSE status of countries/zones, taking into account the notion of risk. The introductory sentence in each category was amended to indicate clearly that the risk to which it refers relates to the cattle population in the country or zone in question.

The articles dealing with international trade in commodities were amended to take into account the terms newly adopted. In addition, other amendments to articles were made as follows:
1) In each article dealing with a commodity likely to spread the causative agent of BSE, the simple reference to the ban on the feeding of ruminants with ruminant-derived meat-and-bone meal was replaced (for statuses with a definition that already imposes the ban) or extended (for statuses with a definition that makes no reference to it) to include a provision referring to the article defining the status of the country or zone from which the commodity comes, so as to ensure that no conditions are overlooked when international veterinary certificates are established.

2) The Ad hoc Group suggested that point 2 b) of Article 2.3.13.10. be deleted, as the OIE should not encourage trade in the oldest cattle, given that the probability of being infected with the BSE agent is highest in this population (the definition of "countries/zones with a minimal risk of BSE" requires the ban on the feeding of ruminants with meat-and-bone meal to have already been in place for at least 8 years).

3) Furthermore, the Ad hoc Group proposed the deletion of paragraph 3 b) of Article 2.3.13.11., as this category provides no guarantee, particularly with countries where the ban on the feeding of ruminants with meat-and-bone meal has only recently been introduced.

4) In Article 2.3.13.11., the words "at least 2 years" were added after "were born" in paragraph 4 b), to take into account the period of time needed to eliminate stocks of potentially contaminated feed in farms.

5) In Articles 2.3.13.11. and 2.3.13.12., the possibility of exporting live cattle from herds where no case of BSE has been reported for at least 7 years was deleted, as it does not provide the same level of security as taking into account the date of birth of the said cattle in relation to the date on which the ban on the feeding of ruminant-derived meat-and-bone meal effectively came into force.

6) With regard to the articles dealing with fresh meat and meat products, a provision was added to ban cattle slaughter techniques at the abattoir that are likely to promote the spread of the BSE agent from the brain to the whole body of the slaughtered animal.

7) Also in regard to fresh meat and meat products, the recommendation not to import mechanically separated meat from the skull and vertebral column of bovine animals, which referred only to countries with a high incidence of BSE, was extended to the other statuses. Furthermore, the question of the possible contamination of these commodities by tissues presenting a risk which was raised at the Conference on BSE in 2001, was taken into account.

8) The problem of contamination referred to above was also taken into account in Article 2.3.13.22. For countries or zones with a moderate BSE risk, the skull and vertebral column were added to the list of tissues presenting a risk as they cannot be entirely cleared of brain and spinal cord tissues, which are already included in the said list.

To date, no satisfactory solution to the problem of surface contamination of carcasses by spinal cord debris during splitting, other than washing the two sides of the carcass. Nothing is known of the risk that might result from such contamination. It is a subject on which further research is required.

The articles dealing with bovine embryos were left virtually unchanged while awaiting the publication of results demonstrating that they do not represent a risk in terms of BSE.

.../Appendices
# List of Participants

## MEMBERS OF THE AD HOC GROUP

<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Institution</th>
<th>Address 1</th>
<th>Address 2</th>
<th>Phone 1</th>
<th>Phone 2</th>
<th>Phone 3</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr M. Dawson</td>
<td>MAFF TSE Research and Surveillance Unit</td>
<td>708 Eastbury House</td>
<td>30-34 Albert Embankment</td>
<td>Tel.: 020 7238 1073</td>
<td>Fax: 020 7238 1095</td>
<td>E-mail: <a href="mailto:Michael.dawson@maff.qsi.gov.uk">Michael.dawson@maff.qsi.gov.uk</a></td>
<td></td>
</tr>
<tr>
<td>Dr. Dagmar Heim</td>
<td>Office vétérinaire fédéral</td>
<td>Etat-Major, Affaires internationales</td>
<td>Case Postale - 3003</td>
<td>Tel.: (41-31) 324 9993</td>
<td>Fax: (41-31) 323 8594</td>
<td>E-mail: <a href="mailto:dagmar.heim@bvet.admin.ch">dagmar.heim@bvet.admin.ch</a></td>
<td></td>
</tr>
<tr>
<td>Dr. John A. Kellar</td>
<td>Disease Surveillance Division</td>
<td>Canadian Food Inspection Agency</td>
<td>NEPEAN</td>
<td>Tel.: (1.613) 228 86 98</td>
<td>Fax: (1.613) 991 69 88 &amp; 228 66 75</td>
<td>E-mail: <a href="mailto:Jkellar@em.agr.ca">Jkellar@em.agr.ca</a></td>
<td></td>
</tr>
<tr>
<td>Dr. S. MacDiarmid</td>
<td>National Manager (Risk Management) Biosecurity Authority</td>
<td>Biosecurity Authority</td>
<td>Ministry of Agriculture and Forestry</td>
<td>Tel.: (64-4) 474 4100</td>
<td>Fax: (64-4) 474 4133</td>
<td>E-mail: <a href="mailto:macdiarmids@maf.govt.nz">macdiarmids@maf.govt.nz</a></td>
<td></td>
</tr>
<tr>
<td>Prof. M. Savey</td>
<td>Directeur de la santé et du bien être des animaux</td>
<td>AFSSA</td>
<td>av. du Général-de-Gaulle</td>
<td>Tel.: (33-0)1 49 77 13 58</td>
<td>Fax: (33-0)1 49 77 90 05</td>
<td>E-mail: <a href="mailto:m.savey@dg.afssa.fr">m.savey@dg.afssa.fr</a></td>
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## OTHER PARTICIPANTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Position/Institution</th>
<th>Address 1</th>
<th>Address 2</th>
<th>Phone 1</th>
<th>Phone 2</th>
<th>Phone 3</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. G. Thomson</td>
<td>(President of the OIE Foot and Mouth Disease and Other Epizootics Commission)</td>
<td>Director of Onderstepoort Veterinary Institute</td>
<td>Agricultural Research Council</td>
<td>Private Bag X6</td>
<td>Onderstepoort 0110</td>
<td>SOUTH AFRICA</td>
<td>Tel.: (27.12) 529 9501</td>
</tr>
<tr>
<td>Dr. A. Thiermann</td>
<td>(President of the OIE International Animal Health Code)</td>
<td>Senior Trade Coordinator</td>
<td>USDA/APHIS</td>
<td>27 Boulevard Du Regent B3</td>
<td>1000 Brussels</td>
<td>BELGIUM</td>
<td>Tel.: (32-2) 508 2762</td>
</tr>
<tr>
<td>Dr. Maura N. Ricketts</td>
<td>Medical Officer</td>
<td>APH/CSR/CD</td>
<td>World Health Organization</td>
<td>20, avenue Appia</td>
<td>1211 Geneva</td>
<td>SWITZERLAND</td>
<td>Tel.: (41-22) 791 3935</td>
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## OIE CENTRAL BUREAU

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<tbody>
<tr>
<td>Dr. T. Chillaud</td>
<td>Head, Information and International Trade Department</td>
<td>OIE</td>
<td>12, rue de Prony</td>
<td>75017 Paris</td>
<td>FRANCE</td>
<td>Tel.: 33-(0)1 44 15 18 88</td>
<td>Fax: 33-(0)1 42 67 09 87</td>
</tr>
<tr>
<td>Dr. F. Crespo León</td>
<td>Chargé de mission Information and International Trade Department</td>
<td>OIE</td>
<td>12, rue de Prony</td>
<td>75017 Paris</td>
<td>FRANCE</td>
<td>Tel.: 33-(0)1 44 15 18 88</td>
<td>Fax: 33-(0)1 42 67 09 87</td>
</tr>
<tr>
<td>Dr. H. Kamakawa</td>
<td>Chargé de mission Information and International Trade Department</td>
<td>OIE</td>
<td>12, rue de Prony</td>
<td>75017 Paris</td>
<td>FRANCE</td>
<td>Tel.: 33-(0)1 44 15 18 88</td>
<td>Fax: 33-(0)1 42 67 09 87</td>
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CHAPTER 2.3.13.

BOVINE SPONGIFORM ENCEPHALOPATHY

Article 2.3.13.0.

The recommendations in this chapter are intended to manage the human and animal health risks associated with the presence of the bovine spongiform encephalopathy (BSE) agent in cattle (Bos taurus and B. indicus) only.

Article 2.3.13.1.

The BSE status of the cattle population of a country or zone can only be determined on the basis of the following criteria:

1) the outcome of a risk analysis assessment identifying all potential factors for BSE occurrence and their historic perspective, in particular:
   a) the potential for introduction and recycling of the BSE agent through consumption by cattle of meat-and-bone meal or greaves of ruminant origin;
   b) importation of meat-and-bone meal or greaves potentially contaminated with a transmissible spongiform encephalopathy (TSE) or feedstuffs containing either;
   c) importation of animals or embryos/ova potentially infected with a TSE;
   d) epidemiological situation concerning all animal TSE in the country or zone;
   e) extent of knowledge of the population structure of cattle, sheep and goats in the country or zone;
   f) the origin of animal waste, the parameters of the rendering processes and the methods of animal feed production;
2) on-going education awareness programme for veterinarians, farmers, and workers involved in transportation, marketing and slaughter of cattle to encourage reporting of all cases of neurological disease in adult cattle;
3) compulsory notification and investigation of all cattle showing clinical signs compatible with BSE;
4) a BSE surveillance and monitoring system with emphasis on risks identified in point 1) above, taking into account the guidelines in Appendix 3.8.3.; records of the number and results of investigations should be maintained for at least 7 years;
5) examination in an approved laboratory of brain or other tissues collected within the framework of the aforementioned surveillance system.

Standards for diagnostic tests are described in the Manual.

Article 2.3.13.2.

[BSE free] Country or zone free of BSE risk

The cattle population of a country or zone may be considered «free of BSE risk» if the following conditions are met:
Appendix II (contd)

1) a risk [analysis assessment, as described in point 1) of Article 2.3.13.1. has been conducted [which demonstrates] and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) either:

   a) there has been no case of BSE; and either:

      i) the criteria in points 2) to 5) of Article 2.3.13.1. have been complied with for at least 7 years; or

      ii) the criteria in point 3) of Article 2.3.13.1. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

   OR

   b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle or bovine embryos/ova, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:

      i) the criteria in points 2) to 5) of Article 2.3.13.1. have been complied with for at least 7 years; or

      ii) the criteria in point 3) of Article 2.3.13.1. have been complied with for at least 7 years and it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants;

   OR

   c) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.1. have been complied with for at least 7 years and the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced for at least 8 years.

   Article 2.3.13.3.

[BSE provisionally free] Country or zone [where no indigenous case has been reported] presumed free of BSE risk

[To be considered as a BSE provisionally free country or zone where no indigenous case has been reported, the country or zone should comply with the following requirements:]

The cattle population of a country or zone may be considered as presumed free of BSE risk should the following conditions be met:

1) a risk [analysis assessment, as described in point 1) of Article 2.3.13.1. has been conducted [which demonstrates] and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;
2) either:
   a) there has been no case of BSE; and either:
      i) the criteria in points 2) to 5) of Article 2.3.13.1. are complied with, but have not been complied with for 7 years; or
      ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.1. have not been complied with for 7 years;
   OR
   b) all cases of BSE have been clearly demonstrated to originate directly from the importation of live cattle or bovine embryos/ova, and the affected cattle as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, have been slaughtered and completely destroyed; and either:
      i) the criteria in points 2) to 5) of Article 2.3.13.1. are complied with, but have not been complied with for 7 years; or
      ii) it has been demonstrated that for at least 8 years no meat-and-bone meal or greaves have been fed to ruminants, but the criteria in point 3) of Article 2.3.13.1. have not been complied with for 7 years.

Article 2.3.13.4.

**Country or zone with a minimal BSE risk** [BSE provisionally free country or zone where at least one indigenous case has been reported]

The cattle population of a country or zone may be considered as presenting a «minimal BSE risk» should the country or zone comply with the following requirements:

1) a risk assessment, as described in point 1) of Article 2.3.13.1., has been conducted and it has been demonstrated that appropriate measures have been taken for the relevant period of time to manage any risk identified;

2) EITHER:

   a) the last indigenous case of BSE was reported more than 7 years ago, the criteria in points 2) to 5) of Article 2.3.13.1. are complied with and the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants is effectively enforced, but:
      i) the criteria in points 2) to 5) of Article 2.3.13.1. have not been complied with for 7 years; or
      ii) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has not been effectively enforced for 8 years;
Appendix II (contd)

OR

b) the last indigenous case of BSE has been reported less than 7 years ago, and the BSE incidence rate, calculated on the basis of indigenous cases, has been less than one case per million during each of the last four consecutive 12-month periods within the cattle population over 24 months of age in the country or zone (Note: For countries with a population of less than one million adult cattle, the maximum allowed incidence should be expressed in cattle-years), and:

i) the ban on feeding ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced for at least 8 years;

ii) the criteria in points 2) to 5) of Article 2.3.13.1. have been complied with for at least 7 years;

iii) the affected cattle as well as:

- if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,

- all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.5.

Country or zone with a moderate [low incidence of] BSE risk

The cattle population of a country or zone may be considered as having presenting a moderate [low incidence of] BSE risks if a risk assessment, as described in point 1) of Article 2.3.13.1., has been conducted, the other criteria listed in Article 2.3.13.1. are complied with, and the BSE incidence rate, calculated over the past 12 months:

1) has been greater than, or equal to, one indigenous case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

2) [calculated as specified in point 1) above] has been less than one indigenous case per million for less than four consecutive 12-month periods;

AND

3) the affected cattle as well as:

a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed.

Countries and zones where the BSE incidence rate [calculated over the past 12 months,] has been less than one indigenous case per million within the cattle population over 24 months of age for at least four consecutive 12-month periods, but where [a risk analysis, as described in point 1) of Article 2.3.13.1., has been conducted which demonstrates that] at least one of the [criteria] other requirements to be [recognised provisionally] considered as presumed free from BSE or as with a minimal BSE risk is not complied with, shall be considered as countries or zones with a moderate [low incidence of] BSE risk.

Article 2.3.13.6.

Country or zone with a high [incidence of] BSE risk

The cattle population of a country or zone may be considered as [having] presenting a high [incidence of] BSE risk if:

1) a risk assessment, as described in point 1) of Article 2.3.13.1., has been conducted, the other criteria listed in Article 2.3.13.1. are complied with, and the BSE incidence rate, calculated over the past 12 months, has been greater than one hundred cases per million within the cattle population over 24 months of age in the country or zone; or

2) the BSE incidence rate, calculated over the past 12 months, has been greater than, or equal to, one case per million and less than, or equal to, one hundred cases per million within the cattle population over 24 months of age in the country or zone, [and] but at least one of the [criteria listed in Article 2.3.13.1.] other requirements to be recognised as with a moderate BSE risk is not complied with.

Article 2.3.13.7.

Regardless of the BSE status of the exporting country, Veterinary Administrations should authorise without restriction the import or transit through their territory of the following commodities:

1) milk and milk products;
2) semen;
3) protein-free tallow (maximum level of insoluble impurities of 0.15% in weight) and derivatives made from this tallow;
4) dicalcium phosphate (with no trace of protein or fat);
5) hides and skins;
6) gelatin and collagen prepared exclusively from hides and skins.
Appendix II (contd)

Article 2.3.13.8.
When importing from a [BSE free] country or zone free of BSE risk, Veterinary Administrations should require:
for all commodities from cattle not listed in Article 2.3.13.7.
the presentation of an international veterinary certificate attesting that the country or zone complies with the conditions in Article 2.3.13.2. to be recognised as free of BSE risk.

Article 2.3.13.9.
When importing from a [BSE provisionally free] country or zone [where no indigenous case has been reported] presumed free of BSE risk, Veterinary Administrations should require:
for cattle
the presentation of an international veterinary certificate attesting that:
1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.3. to be recognised as presumed free of BSE risk;
2) cattle selected for export are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect females.

Article 2.3.13.10.
When importing from a [BSE provisionally free] country or zone [where at least one indigenous case has been reported] with a minimal BSE risk, Veterinary Administrations should require:
for cattle
the presentation of an international veterinary certificate attesting that:
1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.4. to be recognised as with a minimal BSE risk;
2) cattle selected for export:
a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females; [and]
b) [were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years; or
c) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced.

Article 2.3.13.11.
When importing from a country or zone with a [low incidence of] moderate BSE risk, Veterinary Administrations should require:
for cattle
the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be recognised as with a moderate BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) cattle selected for export:
   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females; [and]
   b) [were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years; or
   c) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced.

Article 2.3.13.12.

When importing from a country or zone with a high [incidence of] BSE risk, Veterinary Administrations should require:

for cattle

the presentation of an international animal health certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be recognised as with a high BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) the affected cattle as well as:
   a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
   b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

   if alive in the country or zone, are slaughtered and completely destroyed;

4) cattle selected for export:
   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin and are not the progeny of BSE suspect or confirmed females;
   b) were born at least 2 years after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced [; AND
   c) either were born, raised and had remained in herds in which no case of BSE had ever been confirmed, and which contain only cattle born on the farm or coming from a herd of equal status; or
   d) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years, and which contain only cattle born on the farm or coming from a herd of equal status].
Appendix II (contd)

Article 2.3.13.13.

When importing from a [BSE provisionally free] country or zone [where no indigenous case has been reported] presumed free of BSE risk, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.3. to be recognised as presumed free of BSE risk;

2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for export originate.

Article 2.3.13.14.

When importing from a [BSE provisionally free] country or zone [where at least one indigenous case has been reported] with a minimal BSE risk, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.4. to be recognised as with a minimal BSE risk;

2) ante-mortem inspection is carried out on all cattle from which the meat or meat products destined for export originate;

3) cattle from which the meat or meat products destined for export originate were not slaughtered using pneumatic stunning by injection of compressed air or gas into the cranial cavity or pithing (laceration, after stunning, of central nervous tissue by means of an elongated rod-shaped instrument introduced into the cranial cavity);

4) the fresh meat and meat products destined for export have neither been contaminated by [do not] nor contain either brain [or], eyes [or], spinal cord or mechanically separated meat from skull and vertebral column from cattle over 30 months of age [which were born before the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced].

Article 2.3.13.15.

When importing from a country or zone with a [low incidence of] moderate BSE risk, Veterinary Administrations should require:

for fresh meat (bone-in or deboned) and meat products from cattle
the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be recognised as with a moderate BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) ante-mortem inspection is carried out on all bovines;
4) cattle from which the meat or meat products destined for export originate were not slaughtered using pneumatic stunning by injection of compressed air or gas into the cranial cavity or pithing;

5) the fresh meat and meat products destined for export have neither been contaminated by nor contain, brain, eyes, spinal cord or, distal ileum or mechanically separated meat from skull and vertebral column from cattle over 6 months of age [which were born before the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced].

Article 2.3.13.16.

When importing from a country or zone with a high incidence of BSE risk, Veterinary Administrations should require:

for fresh meat and meat products from cattle

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be recognised as with a high BSE risk;

2) the meat destined for export has been deboned and has neither been contaminated by nor contains [the] tissues listed in point 1) of Article 2.3.13.22. nor nervous and lymphatic tissues exposed during a deboning process;

3) the meat products destined for export are derived from deboned meat and have neither been contaminated by nor contain [no] the tissues listed in point 1) of Article 2.3.13.22. nor nervous and lymphatic tissues exposed during a deboning process, nor mechanically separated meat from skull and vertebral column of bovine animals;

4) a system is in operation enabling the fresh meat and meat products destined for export to be traced back to the establishments from which they are derived;

5) ante-mortem inspection is carried out on all bovines;

6) the cattle from which the meat or meat products destined for export originate:

   a) were identified by a permanent identification system enabling them to be traced back to the dam and herd of origin;

   b) are not the progeny of BSE suspect or confirmed females; [and either:

      i) were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been effectively enforced; or

      ii) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years;]

   c) were not slaughtered using pneumatic stunning by injection of compressed air or gas into the cranial cavity or pithing;

7) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;
Appendix II (contd)

8) the affected cattle as well as:
    a) if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease,
    b) all cattle either born in the same herd as, and within 12 months of the birth of, the affected cattle or reared together with the affected cattle during the first year of their life, and, in both situations, which may have consumed the same potentially contaminated feed as that which the affected cattle consumed during the first year of their life,

if alive in the country or zone, are slaughtered and completely destroyed.

Article 2.3.13.17.

When importing from a [BSE provisionally free] country or zone [where no indigenous case has been reported] presumed free of BSE risk, Veterinary Administrations should require:

for bovine embryos/ova

the presentation of an international veterinary certificate attesting that:

1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.3. to be recognised as presumed free of BSE risk;

2) the embryos/ova were collected, processed and stored in conformity with the provisions of Appendix 3.3.1.

Article 2.3.13.18.

When importing from a [BSE provisionally free] country or zone [where at least one indigenous case has been reported] with a minimal BSE risk, Veterinary Administrations should require:

for bovine embryos/ova

the presentation of an international veterinary certificate attesting that:

1) [the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;] the country or zone complies with the conditions in Article 2.3.13.4. to be recognised as with a minimal BSE risk;

2) embryos/ova destined for export are derived from females which:

   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin;

   b) are not the progeny of BSE suspect or confirmed females;

   c) were not suspected of being affected by BSE at the time of embryo collection;

3) the embryos/ova were collected, processed and stored in conformity with the provisions of Appendix 3.3.1.
Article 2.3.13.19.

When importing from a country or zone with a moderate BSE risk, Veterinary Administrations should require:

for bovine embryos/ova

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.5. to be recognised as with a moderate BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) embryos/ova destined for export are derived from females which:
   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin, and are not the progeny of BSE suspect or confirmed females;
   b) are not affected with BSE;
   c) were not suspected of being affected of BSE at the time of embryo collection; and
   d) either were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced; or
   e) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years;

4) the embryos/ova were collected, processed and stored in conformity with the provisions of Appendix 3.3.1.

Article 2.3.13.20.

When importing from a country or zone with a high BSE risk, Veterinary Administrations should require:

for bovine embryos/ova

the presentation of an international veterinary certificate attesting that:

1) the country or zone complies with the conditions in Article 2.3.13.6. to be recognised as with a high BSE risk;

2) the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced;

3) the affected cattle, as well as, if these are females, their last progeny born within 2 years prior to, or after, clinical onset of the disease, if alive in the country or zone, are slaughtered and completely destroyed;
Appendix II (contd)

4) embryos/ova destined for export are derived from females which:
   a) are identified by a permanent identification system enabling them to be traced back to the dam and herd of origin, and are not the progeny of BSE suspect or confirmed females;
   b) are not affected with BSE;
   c) were not suspected of being affected by BSE at the time of embryo collection; and
   d) either were born after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced; or
   e) were born, raised and had remained in herds in which no case of BSE had been confirmed for at least 7 years, and which contain only cattle born on the farm or coming from a herd of equal status;

5) the embryos/ova were collected, processed and stored in conformity with the provisions of Appendix 3.3.1.

Article 2.3.13.21.

Ruminant-derived meat-and-bone meal or greaves, or any feedstuffs containing such products, which originate from countries with a high incidence of BSE risk should not be traded between countries.

Ruminant-derived meat-and-bone meal or greaves, or any feedstuffs containing such products, which originate from countries or zones not free from BSE risk should not be traded between countries for use in ruminant feed. For other uses, the imported meat-and-bone meal or greaves should have been processed in plants which are approved and regularly controlled by the relevant Veterinary Administration following validation that each plant can achieve the processing parameters described in Appendix 3.6.3. In addition, if originating from a provisionally free country or zone where at least one indigenous case of BSE has been reported with a minimal BSE risk, or from a country or zone with a low incidence of moderate BSE risk, ruminant-derived meat-and-bone meal or greaves, or any feedstuffs containing such products, should comply with the provisions in point 2) of Article 2.3.13.22.

Article 2.3.13.22.

1) The following commodities and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices: brains, eyes, spinal cord, tonsils, thymus, spleen, intestines, dorsal root ganglia, trigeminal ganglia, skull and vertebral column, and protein products derived therefrom, from cattle over 6 months of age originating from countries with a high incidence of BSE risk. Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using these commodities should also not be traded.

2) The following commodities and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices:
   a) brains, eyes, spinal cord, distal ileum, skull, vertebral column and protein products derived therefrom, from cattle, originating from a country or zone with a low incidence of moderate BSE risk, that were born before the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced, and] were at the time of slaughter aged over 6 months;
   b) brains, eyes and spinal cord, and protein products derived therefrom, from cattle, originating from a provisionally free country or zone [where at least one indigenous case of with a minimal BSE risk has been reported, that were born before the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced, and] were at the time of slaughter aged over 30 months.
Food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using the commodities listed in points a) and b) above should also not be traded.

Article 2.3.13.23.

Veterinary Administrations of importing countries should require:

for gelatin and collagen prepared from bones and intended for food or feed, cosmetics, pharmaceuticals or medical devices

the presentation of an international veterinary certificate attesting that:

1) the bones came from a [BSE free] country or zone free of BSE risk, or from a [provisionally free] country or zone presumed free of BSE risk, or from a country or zone with a minimal BSE risk; or

2) the bones came from a country or zone with a [low incidence of] moderate BSE risk; and

   a) skulls and vertebrae (excluding tail vertebrae) have been excluded;

   b) the bones have been subjected to a process which includes all the following steps:

      i) pressure washing (degreasing),

      ii) acid demineralisation,

      iii) prolonged alkaline treatment,

      iv) filtration,

      v) sterilisation at ≥138°C for a minimum of 4 seconds,

or to an equivalent process in terms of infectivity reduction.

Article 2.3.13.24.

Veterinary Administrations of importing countries should require:

for tallow (other than protein-free tallow as defined in Article 2.3.13.7.) intended for food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices

the presentation of an international veterinary certificate attesting that:

1) it originates from a [BSE free] country or zone free of BSE risk, or from a [BSE provisionally free] country or zone presumed free of BSE risk; or

2) it originates from a [BSE provisionally free] country or zone [where no indigenous case has been reported presumed free of BSE risk; or

   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)b) of Article 2.3.13.22.;

   b) if prepared by rendering, (under study); or

3) it originates from a country or zone with a [low incidence of] moderate BSE risk; and

   a) if prepared by fat melting, it originates from cattle which have been subjected to an ante-mortem inspection for BSE with favourable results and has not been prepared using the tissues listed in point 2)a) of Article 2.3.13.22.;
Appendix II (contd)

b) if prepared by defatting of bones:
   i) skulls and vertebral columns have been excluded; or
   ii) it has been processed using a method that reduces the infectivity by at least $5 \log_{10} \text{LD}_{50}/g$ (processes under study);

c) if prepared by rendering, (under study).

Article 2.3.13.25.

Veterinary Administrations of importing countries should require:

for tallow derivatives (other than those made from protein-free tallow as defined in Article 2.3.13.7.) intended for food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices

the presentation of an international veterinary certificate attesting that:

1) they originate from a [BSE free] country or zone free of BSE risk, or from a [provisionally free] country or zone presumed free of BSE risk, or from a country or zone with a minimal BSE risk;

OR

2) they have been produced by hydrolysis, saponification or transesterification using high temperature and pressure.

Article 2.3.13.26.

Careful selection of source materials is the best way to ensure maximum safety of ingredients or reagents of bovine origin used in the manufacture of medicinal products.

Countries wishing to import bovine materials for such purposes should therefore consider the following factors:

1) the BSE status of the country and herd(s) where the animals have been kept, as determined under the provisions of Articles 2.3.13.1. to 2.3.13.6.;

2) the age of the donor animals;

3) the tissues required and whether or not they will be pooled samples or derived from a single animal.

Additional factors may be considered in assessing the risk from BSE, including:

4) precautions to avoid contamination during collection of tissues;

5) the process to which the material will be subjected during manufacture;

6) the amount of material to be administered;

7) the route of administration.
APPENDIX 3.8.3.

SURVEILLANCE AND MONITORING SYSTEMS FOR BOVINE SPONGIFORM ENCEPHALOPATHY

Article 3.8.3.1.

Introduction

The surveillance strategy applied for bovine spongiform encephalopathy (BSE) should be determined by, and commensurate with the outcome of the risk assessment referred to in article 2.3.13.1. Surveillance and risk assessment are part of an iterative process and inform each other.

Surveillance for BSE has at least two goals: one is to determine whether BSE is present in the country, and the other, once the disease has been detected, is to monitor the evolution of the epizootic, direct control measures and monitor their effectiveness.

A surveillance strategy must combine a number of methods of investigation.

Surveillance for bovine spongiform encephalopathy (BSE) requires the laboratory examination of cattle brains or spinal cord by samples in accordance with the methods described in the Manual.

For surveillance purposes, testing a part of the population is consistent with Chapter 1.3.5. on surveillance and monitoring of animal health. Recommended strategies for selecting the part of the population for testing are described below.

Article 3.8.3.2.

Examination of native-born cattle displaying clinical signs compatible with BSE

Screening the cattle population for animals displaying compatible clinical signs is the best approach for increasing the ability to detect BSE if it occurs. With this approach, animals Cattle affected by illnesses that are refractory to treatment, and displaying progressive behavioural changes such as excitability, persistent kicking when milked, changes in herd hierarchical status, hesitation at doors, gates and barriers, as well as those displaying progressive neurological signs or moribund cattle without signs of infectious or traumatic illness are candidates for examination. Since BSE causes no pathognomonic clinical signs, all countries with cattle populations will observe individual animals with compatible clinical signs. Examination of the brains of these cattle may identify alternative diagnoses such as cerebral listeriosis, rabies or brain tumor. Surveillance should primarily focus on cattle over 24 months of age, but younger cattle should not be ignored. display behavioural and neurological signs lasting for at least 15 days and resistant to treatment. In countries where the incidence of progressive neurological diseases is low, surveillance may be extended to cattle over 4 years of age presenting clinical signs of progressive diseases.

Table 1 indicates the minimum number of clinical cases that should be subjected to diagnostic tests according to the total native-born cattle population over 24 months of age. As this sampling is not random, the numbers indicated in this table are a subjective interpretation rather than a strict statistical deduction.
Appendix III (contd)

Table 1. **Minimum number of annual investigations of animals showing clinical signs compatible with BSE required for effective surveillance according to the total native-born cattle population over [24] 30 months of age**

<table>
<thead>
<tr>
<th>Total [native-born] cattle population over [24] 30 months of age</th>
<th>Minimum number of [brains] samples to examine</th>
</tr>
</thead>
<tbody>
<tr>
<td>500,000</td>
<td>50</td>
</tr>
<tr>
<td>700,000</td>
<td>69</td>
</tr>
<tr>
<td>1,000,000</td>
<td>99</td>
</tr>
<tr>
<td>2,500,000</td>
<td>195</td>
</tr>
<tr>
<td>5,000,000</td>
<td>300</td>
</tr>
<tr>
<td>7,000,000</td>
<td>336</td>
</tr>
<tr>
<td>10,000,000</td>
<td>367</td>
</tr>
<tr>
<td>20,000,000</td>
<td>409</td>
</tr>
<tr>
<td>30,000,000</td>
<td>425</td>
</tr>
<tr>
<td>40,000,000</td>
<td>433</td>
</tr>
</tbody>
</table>

**Article 3.8.3.3.**

Examination of [additional selected subpopulations] targeted cattle not displaying clinical signs compatible with BSE

[To increase the ability to detect BSE if it is present, the following additional selected subpopulations should be examined:

a) cattle imported from countries or zones not free from BSE, animals which have consumed potentially contaminated feedstuffs from countries or zones not free from BSE, offspring of BSE affected cows and animals which have consumed feedstuffs potentially contaminated with other TSE agents;

b) cattle that have died or have been killed for reasons other than routine slaughter (including 'fallen' stock and emergency slaughter) should be examined. Surveillance needs to focus on animals over [24] 30 months of age.

**Article 3.8.3.4.**

Examination of cattle subject to normal slaughter

In countries known to be infected with BSE, sampling at routine slaughter is a means of monitoring the progress of the epizootic and the efficacy of control measures applied, because it offers continuous access to a cattle population of known class, age structure and geographical origin.

Exclusive dependence on random sampling [of brains or spinal cords] from normal cattle is not recommended, unless [a huge] the number of samples [is] examined annually is statistically sufficient. Since BSE is rare, even in countries with the highest incidence of disease, microscopic examination of brains or spinal cords from a random sample of the national cattle population is unlikely to detect a disease prevalence of 1 in 1,000,000 [or more unless huge numbers of [brains or spinal cords] samples are examined].
Article 3.8.3.5.

(former point 2)a) Within each of the above sub-populations, countries may wish to target cattle identifiable as imported from countries or zones not free of BSE risk, animals which have consumed potentially contaminated feedstuffs from countries or zones not free from BSE, offspring of BSE affected cows and animals which have consumed feedstuffs potentially contaminated with other TSE agents.
TENTATIVE APPROACH TO MATCH THE DIFFERENT BSE STATUS DESCRIBED IN THE BSE CODE CHAPTER WITH THE GUIDELINES ON SURVEILLANCE INCLUDED IN THE APPENDIX

On the basis of empirical evidence from some countries infected with BSE, it has been determined, based on the application of the same diagnostic test to three sub-populations within the same country, that there is a marked but consistent difference among the relative effectiveness of the testing regimens (in parallel country to country) among the three diagnostic regimens, where the diagnostic regimen = [diagnostic test] applied to [sub-population].

The following table reflects the relative effectiveness of each testing regimen in reaching the required level of credits in order to support the claim for inclusion within a BSE status category:

One investigation of animals showing clinical signs compatible with BSE equals Y investigations of targeted cattle not displaying clinical signs compatible with BSE and equals Z investigations of cattle subjected to normal slaughter.