EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate B - Scientific Health Opinions
Unit B1 - Monitoring and dissemination of scientific opinions

OPINION OF THE SCIENTIFIC STEERING COMMITTEE

ON THE SCIENTIFIC GROUNDS OF THE

ADVICE OF 30 SEPTEMBER 1999 OF THE FRENCH FOOD SAFETY AGENCY (THE *AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES ALIMENTS*, AFSSA), TO THE FRENCH GOVERNMENT ON THE DRAFT DECREE AMENDING THE DECREE OF 28 OCTOBER 1998 ESTABLISHING SPECIFIC MEASURES APPLICABLE TO CERTAIN PRODUCTS OF BOVINE ORIGIN EXPORTED FROM THE UNITED KINGDOM.

ADOPTED AT ITS MEETING OF

28-29 OCTOBER 1999

(EDITED FOLLOWING A WRITTEN PROCEDURE (30.10 - 15.11.99)

AND RE-EDITED AT THE SSC MEETING OF 9-10 DECEMBER 1999)

Opinion of the Scientific Steering Committee

on the scientific grounds of the

Advice of 30 September 1999 of the French Food Safety Agency (the *Agence Française de Sécurité Sanitaire des Aliments,* AFSSA), to the French Government on the draft Decree amending the Decree of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom.

Abbreviations used in this document (selection):

AFSSA:	*Agence Française de Sécurité Sanitaire des Aliments* (the French Food Safety Agency*)*
BSE:	Bovine Spongiform Encephalopathy
CEA:	Commissariat à l'Energie Atomique
CNS:	Central Nervous System
DBES:	Date Based Export Scheme
ECHS:	Export Certified Herd Scheme
GB:	Great Britain
MAFF:	Ministry of Agriculture, Fisheries and Food (UK)
MBM:	Meat-and-bone meal
OIE:	Office International des Epizooties (World Organisation for Animal Health – *Organisation Mondiale de la Santé Animale*)
OTMS:	Over Thirty Months Scheme
PrP ^{res}:	pathological isoform of the prion protein (PrP^{Sc} in part of the scientific literature).
SBO:	Specified bovine offals
SEAC:	Spongiform Encephalopathy Advisory Committee (UK)
SRM:	Specified Risk Materials
SSC:	Scientific Steering Committee
TSE:	Transmissible Spongiform Encephalopathy

1. Mandate

Following the AFSSA advice, the European Commission's questions submitted to the SSC were:

1. Do the opinions and documentation provided by the French authorities contain scientific information, epidemiological data or other evidence that has not been taken into account by the SSC?
2. If, in the above documentation, there is new information, data or evidence, or if the SSC has at its disposal any such new information, would this require a re-examination of any of the four SSC Opinions directly related to the scientific rationale of the DBES?
3. In the light of the answers to the above question, could the SSC confirm (or not) its position that the conditions of the DBES, if appropriately respected, are satisfactory with regard to the safety of the meat and meat-products produced?

2. Background

The original UK proposal of 2 October 1997 refers to the OIE Code[1] requiring, in relation to the export of meat (including products derived therefrom) from a country or zone with a high incidence of BSE, that:

a) the meat must come from animals which were born and retained in herds in which no case of BSE had been recorded, or**,**

b) the meat must come from animals born after the ban on the use of ruminant meat-and-bone meal was effectively enforced.

The first option had been addressed in the Export Certified Herd Scheme (ECHS), which was previously submitted by the UK for approval and was the subject of a scientific opinion by the Scientific Veterinary Committee in 1997.

The second option was addressed in the Date Based Export Scheme (DBES) (see annex 1). The key elements of the scheme were an effective feedban (from 1.08.96) designed to exclude feedborne transmission and an offspring cull combined with confirmation of survival of the dam for 6 months, designed to significantly reduce maternal transmission. As both known routes of transmission were considered to be covered, the DBES did not include a requirement for herd freedom from BSE as originally proposed in the ECHS.

On 9.12.97, the SSC adopted the *Report on the UK Date Based Export Scheme (DBES) and the UK proposal on Compulsory Slaughter of the Offspring of BSE Cases (*re-edited on 23.01.98), accepting in general the scientific soundness of the Scheme, but making a number of additional requirements.

These were addressed in the SSC Opinion of 20.02.98 *On the revised version of the UK Date Based Export Scheme and the UK proposal on compulsory slaughter of the offspring of BSE-cases, submitted on 27.01.98 by the UK Government to the European Commission.*

In addition, in relation to the UK DBES, the SSC adopted the following 2 opinions:

a. Opinion on *The safety of bones produced as by-product of the Date Based Export Scheme,* adopted, 23.10.98:
b. Opinion on *Monitoring Some Important aspects of the evolution of the Epidemic of BSE in Great-Britain (Status, April 1999),* adopted, 28.05.99.

Finally, the SSC adopted a number of opinions of indirect relevance, for example on specified risk materials (SRMs), vertical transmission of BSE, safety of products and geographical BSE risk.

As a result of these opinions, the decision to authorise the export of deboned meat and products derived therefrom under the DBES was adopted on 25 November 1998 (Commission Decision N° 98/692/EC) and the date when the export could commence was set at 1 August 1999 by Commission Decision 1999/514/EC, following the favourable outcome of a Community mission, in April 1999.

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[1] The details are provided in the OIE Code on BSE . It is noted that since then new versions of the OIE Code with respect to BSE have been adopted and that at its meeting of 13-16 September 1999, the OIE Bureau reviewed the recommendations received from an OIE *ad hoc* Group, which prepared an updated draft Code. This will be discussed at the next OIE Code plenary meeting in May 2000.

On 30 September 1999 AFSSA issued an opinion which challenged the EU Decision of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom.

This AFSSA advice of the 30th September is based on the Opinion of 30 September 1999 of the French Group of Experts on Transmissible Sub-acute Spongiform Encephalopathies regarding the lifting of the UK Export ban. This Group of Experts has the same membership as the former Inter-ministerial Committee for Transmissible Suc-acute Spongiform Encephalopathies, established in 1996. In addition, the latter Committee adopted on 1 July 1999 an opinion on the BSE Epidemic in the UK.

The main points on which the Opinion of 30 September 1999 of the French Group of Experts on Sub-acute Spongiform Transmissible Encephalopathies is based, were summarised as follows:

a) Much more sensitive tests are emerging that allow the finding of PrP^{Res} in tissues in which no infectivity has been detected so far.

b) The similarity of the number of confirmed cases reported in UK in the period January to end of August 1998 and 1999, suggests an unexplained slow down of the rate of decrease.

c) The availability of the post-mortem BSE-tests evaluated by the Commission.

d) The results from additional surveillance programmes (i.e., in the UK: brain histopathology of bovines slaughtered under the Over Thirty Months Scheme (OTMS); in Switzerland: the *Prionics* test, if necessary confirmed by histology or immunocytochemistry on all adult cows in fallen stock, emergency slaughters and a sample of routinely slaughtered adult cows).

e) Doubts on the traceability of meat products.

3. Elements of discussion

The 3 questions submitted to the SSC by the European Commission were first discussed at two meetings of the SSC's TSE/BSE *ad hoc* Group (14 October 1999 and 25 October 1999)[2]. The *ad hoc* Group discussed the following 4 points:

a) The possibility of verifying the distribution of PrP^{res} in the various body tissues and fluids of infected (incubating) cattle. Linked to this was the question of the usefulness of increasing sensitivity of the BSE laboratory tests and assays.

b) The evolution in 1999 of the epidemiology of the disease in the UK and its importance for the DBES, and linked to it, the issue of possible new transmission routes.

c) The potential of the recently evaluated rapid diagnostic BSE-tests and of new analytical possibilities with regard their use in surveillance and monitoring of TSEs.

d) The traceability of the meat and meat products.

[2] The *ad hoc* Group meeting of 25 October 1999 was attended partly by invited scientists from the UK and France observers, with the status of observer.

As to date, the SSC was given detailed information on the analyses and deliberations of the TSE/BSE *ad hoc* Group, together with the data on the UK epidemic as of mid-October 1999, new input on epidemiological analyses of BSE including projections of cases in the DBES herd and also the most recent data from SEAC from cattle-to-cattle experiments on the possible infectivity of muscle, spleen and lymph nodes. The SSC had also access to other recent scientific material such as the Notes of the Tübingen Conference on *Characterisation and Diagnosis of Prion Diseases in Animals and Man* (23-25 September 1999) and other recent papers.

3.1. New tests for PrP^{res} and an assessment of the distribution PrP^{res} in different organs

The SSC reassessed the usefulness of new methods which promise to provide ever more sensitive ways for documenting the distribution of PrP^{res} of different TSEs in the organs of different species.

These methods, e.g., the one developed by Schmerr *et al* (see also: Notes of the Tübingen Conference), use different techniques which may lead ultimately to assays approaching the possibility to even detect a single protein. The question was raised as to how far this would be relevant with respect to the potential infectivity of bovine tissues containing very low concentrations of PrP^{res} for animals and in particular for man.

It was recognised that some recently published research using sensitive tests has documented the distribution of injected PrP^{res} into different organs in species which normally do not manifest the clinical disease. Thus, there may be a need to distinguish between the mere presence of PrP^{res}, its capacity to replicate and its ability to cause disease. The presence of low concentrations of PrP^{res} can be a feature of the distribution characteristics after parenteral administration or oral exposure and has not necessarily an implication of infectivity. The sensitivity of current methodologies is such that the failure to find PrP^{res} at currently detectable concentrations, however, does not necessarily guarantee the true absence of PrP^{res}. When tests indeed detect the presence of PrP^{res} aggregates in naturally infected animals, it is reasonable to infer that the TSE transmitted to the particular species has probably replicated and may eventually lead to clinical disease.

Three recent *post mortem* diagnostic tests evaluated by the EC on material from the brain of BSE clinically diseased animals have been shown to be robust in assessing clinical cases of BSE. Dilution experiments also imply that one or more of these tests may prove valuable in detecting PrP^{res} replication before the development of the clinical disease. (see also Section 3.4).

The SSC concludes that new and more sensitive tests may well highlight the presence of the BSE agent in different cattle tissues long before clinical disease develops. Whether the presence of extremely low levels of detectable PrP^{res} indicate infectivity for man is a different issue which is being considered by the SSC.

Until such time as the biological significance of the newly developed, highly sensitive molecular assays becomes clearer, the SSC has no basis for changing its approach, especially as it has accumulated considerable experience and historical

control data using established methodologies. The SSC would need to acquire control data for the alternative methodology before changing. The SSC from its first analyses of risk has used data from infection studies in different systems to estimate the relative risk of the BSE agent load in different tissues at different stages of the infection cycle.

3.2. Organ distribution: the importance of considering both the type of TSE agent and the species affected.

The SSC took account of recent studies e.g. by Schmerr *et al* (1999)[3], Maingien *et al* (1999)[4], Wells *et al* (1998, 1999)[5,6] which follow the distribution of different TSE agents in different species. The SSC was also informed of preliminary[7] research found to indicate the presence of PrP^{res} during the first months of life after birth in lymphoid organs of sheep born to a scrapie infected ewes. Recent analyses show the importance of establishing the specificity of pathogenic processes whereby one TSE e.g. a scrapie strain establishes itself in a particular host, whereas another TSE e.g. BSE or even other scrapie strains either have no effect or induce a different pathological process. Transgenic models are being used to distinguish between the scrapie agents and the BSE agent. These models may eventually prove helpful in distinguishing between the scrapie and BSE agents when examining the basis of spongiform encephalopathies in sheep. Thus, it would be possible to establish whether a scrapie-like illness in sheep is in practice caused by the BSE rather than by a scrapie agent.

A further issue considered was the current bioassay distinction between the infectivity of the BSE agent in sheep and cattle. Using the mouse bioassay system, two sheep, one challenged orally and another i/c with BSE, were found to have infectivity in the spleen. Tissues other than brain and spleen were not tested, but the distribution of BSE in sheep through the peripheral tissues and the lymphatic system may prove to be similar to scrapie when further studies are undertaken. By contrast, no bioassay – either with mice or with cattle, the most sensitive bioassay

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3 **Schmerr, M.J., Jenny, A.L., Bulgin, M.S., Miller, J.M., Hamir, A.N., Cutlip, R.C., Goodwin, K.R., 1999.** Use of capillary electrophoresis and fluorescent labelled peptides to detect the abnormal prion protein in the blood of animals that are infected with a transmissible spongiform encephalopathy. Journal of Chromatography A, **853**, 207-214.

4 **Maingien, T., Lasmézas, C.I., Beringue, V., Dormont, D., Deslys, J.P., 1999**. Pathogenesis of the oral route of infection of mice with scrapie and bovine encephalopathy agents. Journal of General Virology.

5 The protocol is described in: http://www.maff.gov.uk/animalh/bse/bse-science/level-4-pathog.html.

6 **Wells, G. A. H., Hawkins, S. A. C., Green, R. B., Austin, A. R., Dexter, I., Spencer, Y. I., Chaplin, M. J., Syack, M. J., Dawson, M., 1998.** *Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update.* Veterinary Record, **142,** 103-106.

Wells, G. A. H., Hawkins, S. A. C., Green, R. B., Spencer, Y. I., Dexter, I., Dawson, M., 1999. Limited detection of sternal bone marrow infectivity in the clinical phase of experimental bovine spongiform encephalopathy. Veterinary record, **144**, 292-294.

7 The data and results were not available to the SSC.

system yet devised, i.e. i/c (intra-cerebrally) infection in cattle - has documented BSE infectivity in the spleen of cattle suffering from clinical BSE.

These data might be taken to imply that the pathological process of the BSE agent migration in cattle is different from the spread of the scrapie agent or even of the BSE agent in sheep. However, the SSC had not come to that conclusion because it is possible that more sensitive tests would show that the BSE agent can occur in the lymphatic tissues and blood of cattle orally infected with the BSE agent relatively early in the incubation period, although current bioassays have not revealed infectivity in these tissues. The SSC notes that its original cautious approach to the designation of BSE infectivity in cattle (opinion of 9.12.1997) presupposed that the behaviour of the BSE agent in cattle could parallel that of scrapie in sheep. If more sensitive assays can be applied to blood, lymphatic tissues, peripheral nerves and other organs of BSE affected cattle and sheep then a more coherent view can be obtained of whether the BSE agent behaves in the same way in sheep and cattle. The SSC would recommend that this research be promoted.

The SSC - in its various opinions related to tissue infectivity (e.g., on Specified Risk Materials, 9.12.97); on the safety of bones as a by-product of the DBES (23.10.98), on vertical transmission of BSE (March 1999)) - also used the most recent results, provided by MAFF, of the still ongoing pathogenesis experiment. This experiment [8,9] started in April 1992, is based on oral cattle-to-cattle transmission with 100 grams of contaminated bovine brain material, i.e., a test system with no species barrier. Mice were then inoculated i/c with preparations of various tissues taken from the infected but pre-clinical cattle at different intervals after oral exposure. Thus far, none of the tissues which were found (in 1998) to be without infectivity, have led to clinical disease.

In another bioassay, some of these tissues from orally exposed cattle are also being re-inoculated i/c into cattle. This test is the most sensitive bioassay of infectivity currently available with incubation times for the clinical manifestation of the disease which are shorter than the time for oral dose to induce the clinical state. Thus dilutions of infected brain, diluted 10^{-3} to 10^{-7} have average incubation times to disease up to date of 24 to 42 months. Cattle challenged with spleen taken from cattle killed 10 and 26 months post oral exposure now show no disease 15 and 7 months later. Cattle were also challenged with pooled muscle tissue comprising muscles from head, thoracic region and leg (masseter, longissimus dorsi, semitendinosus). The muscles from cattle killed 18 months post challenge, were inoculated i/c into further cattle. These cattle are now, 36 months post inoculation,

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8 The protocol is described in: http://www.maff.gov.uk/animalh/bse/bse-science/level-4-pathog.html.

9 **Wells, G. A. H., Hawkins, S. A. C., Green, R. B., Austin, A. R., Dexter, I., Spencer, Y. I., Chaplin, M. J., Syack, M. J., Dawson, M., 1998.** *Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update.* Veterinary Record, **142,** 103-106.

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without clinical disease. Similarly, muscles from cattle killed 32 months post challenge, were inoculated i/c into further cattle. At this stage (32 months), the CNS of the orally infected cattle from which the muscles were taken were shown to contain infectivity in the mouse bioassay. Recipient cattle are now, 35 months post inoculation, and without clinical disease. The SSC therefore notes that muscle tissue has never been found to be infective, even from BSE cattle in the later stages of infection, in spite of the fact that peripheral nerves, lymphatic tissue and blood are associated with muscle.

In yet another experiment, lymph node and spleen homogenates taken from cattle with confirmed BSE, were inoculated i/c into healthy cattle. Today, 80 months post challenge, they are all free of clinical disease. Given that the average incubation period of naturally exposed, i.e., orally infected cattle is 4 to 5 years, this experimental data with intra-cerebral challenge and an incubation period of 6½ years is strongly suggestive of no infectivity associated with the lymph nodes and spleen in orally infected cattle. This therefore now provides important evidence in favour of a difference in the routes of spread of both scrapie strains and BSE infectivity in sheep compared with the spread of BSE in cattle.

3.3. Epidemiology

In its opinion of July 1st 1999, the French Inter-Ministerial Committee on Transmissible Sub-acute Spongiform Encephalopathies issued an opinion on the pattern of decline in the UK epidemic of BSE. It compared the number of cases recorded by OIE in 1996, 1997 and 1998 with estimated numbers of cases and estimated range (95% confidence intervals) of cases to the models of Anderson *et al* (1996) and Donnelley *et al* (1997). The Expert Group on Transmissible Sub-acute Spongiform Encephalopathies issued a further opinion on September 30th 1999, on this topic. The opinion drew the attention of the AFSSA to the following: "*The increasingly limited decline in prevalence in Great Britain, despite measures taken, begs the question as to whether we understand all the possible origins of contamination*". The group also points out that, in this regard, they had access to data on the UK epidemic as of July 1999.

This issue has been the subject of an SSC opinion and has formed a significant part of the SSC agenda and discussions at its plenary meetings. In May 1999, the SSC adopted an opinion on "*Monitoring some important aspects of the evolution of the epidemic of BSE in Great Britain*". The SSC drew attention to the fact that for 1998 (the most recent year for which complete data were available), the upper 95% confidence limits of the UK Veterinary Laboratory Agency model appeared to be closer to the observed cases than the central estimate. Nonetheless, the SSC concluded that: "The current and expected cases of BSE in the United Kingdom are in line with all models, but that the tail of the epidemic will not necessarily present a constant decline, certainly not when small numbers are involved".

Within the herd, animals born after the 1st of August 1996 which otherwise comply with the DBES criteria, are still alive, e.g., breeding stock, dairy cattle. The SSC recommends that consideration be given to prioritising these animals in any surveillance scheme involving both the newly available and other tests and asks the Commission services to examine the statistical aspects of such ~~a~~ priority surveillance as well as its practical feasibility.

In general terms, since the opinion of May 1999, the SSC has sustained its wish to be kept fully up to date on the area of UK surveillance of the incidence of BSE. The SSC expressed its wish to be kept informed in quasi-real time about further results of this and similar surveys, as they become available. At its meeting of 28-29 October 1999, members were provided with a copy of the UK MAFF's most recent preliminary results of a survey of BSE reported incidence in OTMS cattle.

The AFSSA was using data on confirmed cases of BSE and care needs to be taken to assess comparable information. Confirmed cases amount to 70 to 80% of the number of "restricted" animals specified by veterinarians as potential cases of BSE. Once restricted, there may be a delay before slaughter in order to assess any further clinical developments and then, after slaughter, brain and other tissues have to be removed for later diagnostic tests. It may therefore take several months for a restricted case to be confirmed as a BSE clinically affected animal. This means that 1999 confirmed cases often relate to reporting and restriction of animals in 1998 and many cases are still awaiting diagnosis (see annex). The delays can confuse comparisons between years. The SSC therefore used the most up to date figures obtained from MAFF (status: mid-October 1999) by comparing restricted cases month by month and year by year. When this is done, the picture is clearer. The SSC concluded that the decreasing trend of the numbers of BSE cases is confirmed, although the post-1996 decrease is less sharp (as previously noted in its opinion of May 19th last) than for the pairs of years 1994/1993, 1995/1994, 1996/1995. The SSC obtained analyses of these data using different epidemiological models of the BSE epidemic in the UK. All reported that the decline in the UK epidemic is within the upper limits of confidence of model predictions. It is important to note that these comparisons between observed and predicted number of cases were based, as it should be, on comparing like with like.

The SSC noted several possible reasons to explain the slower decrease in the epidemic. The SSC concluded that, at present, no scientific evidence is available pointing towards the existence of another route of transmission than through contaminated feed or via maternal transmission. However, a third mechanism cannot be excluded a priori, although if such a mechanism is present, it must, in quantitative terms, be of minor significance compared with the two recognised routes of infection.

In January 1998, the UK MAFF submitted to the Commission, following the request of the SSC, an assessment of the number of animals that might possibly be infected by maternal transmission and which may eventually be included in the DBES. The results of this assessment were summarised in the SSC's opinion of February 1998. In the preparation of the present opinion, the Secretariat asked for an update of the risk assessment. It appears that in the year 1998/1999, under a worst case scenario, theoretically 39 eligible animals out of a total of approx. 2,250,000 animals slaughtered for beef production, may be maternally infected (assumption: 10% maternal transmission during the last pre-clinical 6 months of BSE incubation). From these animals, it is assumed that a subgroup of approx. 75,000 animals would be exported under the DBES during the first year of resumed exports (increasing to 150,000 in the 3rd year of export). A higher proportion of this sub-group will have been grass-fed than the rest of the UK herd and will therefore be at much lower risk of feed-borne infection and consequent

maternal transmission. Not allowing for this, a worst case scenario means that possibly 1.3 infected animals (per 75,000) would be eligible for export in 1998/99. However such animals would be younger than 30 months with its SRMs and certain other tissues removed, as well as being deboned. The corresponding figures for 1999/2000, 2000/2001 and 2001/2002 are 26, 15 and 13 beef animals slaughtered in the UK, or approximately 0.85 (per 75,000) exported potentially infected animal carcass next year with a probability of less than 1 animal in subsequent years even if exports increase substantially.

This analysis therefore means that with UK animals born after August 1st 1996 the risk of having an exported animal incubating BSE after oral feeding of residual MBM should be zero. At most one animal may be incubating BSE having been infected by maternal transmission. These figures are remarkably different from the headline figures for BSE cases in Britain because these other figures relate to older cohorts of animals which cannot, unlike the rest of the animals in the EU, enter the food chain. It is therefore misleading to compare these UK figures with those of other EU Member States (see table of BSE reports for different countries in annex). The timing of the UK feed ban measures and the special 30 month rule mean that there is a different spectrum of risk in the DBES from that suggested by the overall incident figures for BSE. On these grounds the SSC concludes that it is reasonable to consider the risk from UK DBES meat and its products as safe as similar food derived from other Member States.

In regard to the issue of the AFSSA's opinion on the value of newly developed tests for the detection of BSE in clinically affected animals, the SSC has previously expressed the view that such tests may play a key role in the detection of BSE cases in animals with a high risk of developing BSE e.g., animals over 30 months of age (opinion of May 1999).

3.4. The post mortem tests for diagnosing BSE

Three rapid tests in bovines have been shown by the European Commission (European Commission, 1999, *The Evaluation of Tests for the Diagnosis of Transmissible Spongiform Encephalopathies in Bovines* - see DG-SANCO internet site) to have excellent potential (high sensitivity and specificity) for detecting or confirming clinical BSE for diagnostic purposes or for screening dead or slaughtered animals, particularly casualty animals or carcasses to be used for rendering.

The above tests are

- *Prionics*: an immuno-blotting test based on a western blotting procedure for the detection of the protease-resistant fragment PrP^{Res} using a monoclonal antibody
- *Enfer*: a chemiluminiscent ELISA, using a polyclonal anti-PrP antibody for detection
- *CEA*: a sandwich immunoassay for PrP^{Res} carried out following denaturation and concentration steps. Two monoclonal antibodies are used.

These tests are rapid (less than 24 hours) and some of these tests may have a detection limit at least comparable to that of the mouse bioassay. The application

of these new BSE-tests on the basis of an approach similar to the one applied in Switzerland (e.g. fallen stock, emergency slaughters and a sample of routinely slaughtered adult cows) would be useful for better estimating the prevalence of BSE-cases in older animals in the late 1990s, not only in UK but also in other Member States, and for eventually estimating the incidence of BSE infection in bovines born after 1 August 1996 in the UK.

The ability of these tests to detect low concentrations of PrP^{res} gives grounds for the possibility that they might be able to detect infected animals before the development of clinical signs. However, further work is necessary before the usefulness of the above tests in pre-clinical screening programmes can be assessed.

Work advancing laboratory test methodologies should be particularly focused on an in-depth scientific assessment of their applicability (e.g. sensitivity, specificity, test detection limit, sample size required, interpretation of results) to target populations (e.g. certain age classes) other than clinically diseased animals.

The possible application of the new diagnostic tests in UK cattle born after 1 August 1996 in this context was discussed, particularly in the context of the opinion expressed by AFSSA in this regard: "*within a few months the screening tests being developed, and recently validated by the European Commission (…), should provide vital information above all on the proportion of contaminated animals among the group born in 1996 and 1997*". In view of the expected low infection incidence, a very large number of DBES bovines would have to be tested for 'nil positives' to be genuinely informative about the prevalence of infected animals. Moreover, given the large number required and the fact that the tests are not yet validated for pre-clinical stages, great care should be taken to avoid an unjustified assumption of safety or danger if false negatives and/or false positives occur. The statistical credentials for such a programme would need to be developed, as well as its feasibility. Nonetheless, these tests along with other diagnostic measures may provide an insight into the scientific aspects of the pathogenesis of BSE although they may not as yet be appropriate in risk-management strategies.

3.5. Controls and traceability

The SSC agreed that the existence of an effective and safe system for the identification and tracing particularly of meat products is of crucial importance. However, this is a control or risk management and not a scientific issue. The SSC was informed that the meat products exported under the DBES scheme must be produced in dedicated plants handling only export eligible meat (meaning bovine meat complying with the DBES, ECHS or of foreign origin).

So far, the UK has not approved plants for the export of processed meat under the DBES. At the moment, one slaughterhouse and cutting plant in Cornwall and one slaughterhouse and cutting plant in Scotland are approved for export under the DBES.

The SSC also noted that the UK has agreed not to approve any meat processing plants under the DBES without prior inspection by the Food and Veterinary Office of the EC. No meat processing plants were presented for inspection in April, when the final inspection before setting the date was carried out.

The SSC considers that the control and traceability of DBES meat and meat products are not within its mandate.

4. Opinion

Preambles:

a. The SSC considers that the issue of safety with respect to BSE should be considered in the context of the protection of public health at the level of all the Member States of the European Union. The SSC stresses that the risk of human exposure in the UK was reduced to a minimum as a result of an extensive series of measures implemented as the epidemic evolved.

The SSC, on 23 January 1998 adopted an opinion on *Defining the BSE risk for specified geographical areas*. Regarding the assessment of the risk of humans being exposed to the BSE agent, three interlinked risks were considered to be of major importance:

- Incident risk: probability that an infectious animal (or materials thereof) enters the food and/or feed chains.
- Propagation risk: probability that an initial infection is propagated within the system of a given region and within a given time period.
- Human exposure risk: probability that a human being is exposed to an infective dose of the BSE agent, within a given time period.

The factors contributing to the incident and propagation risks in a geographical area were listed as (1) Structure and dynamics of the cattle, sheep and goat populations, (2) Animal trade, (3) Animal feed, (4) Meat and bone meal (MBM) bans, (5) Specified bovine offals (SBO) and Specified Risk Materials (SRM) bans, (6) Surveillance of TSE, with particular reference to BSE and scrapie, (7) Rendering and feed processing and (8) BSE and scrapie related culling.

b. The scientific understanding of TSEs is continuously evolving and new findings become regularly available. The SSC, its TSE/BSE *ad hoc* Group and the more than 40 additional scientists who have so far participated in their various working groups have monitored these new scientific data. It formed the basis for more than 30 BSE-related opinions adopted since December 1997.

In the present opinion, a number of recent new developments have been addressed. They are or will also be addressed in a number of working groups, for example on *Human Exposure Risk* (established in 1998), *Human Exposure Limit Line* (established in March 1999) and *Safety of ruminant blood* (established at the SSC meeting of 16-17 September).

The SSC will continue its active monitoring and analysis of risks associated with BSE in Europe and the rest of the world. It will further monitor the evolution of the BSE epidemic in Great Britain, which has led to an opinion of the SSC in May 1999 and which will be updated in the light of the most recent data provided by the UK authorities, the complementary analyses carried out

by the TSE/BSE *ad hoc* Group and the SSC, the more recent models and their outputs that became available since May 1999, the more recent data on the pathogenesis of BSE in the UK experiments and the projected numbers of potential cases in animals under 30 months of age.

4.1. Question 1

Do the opinions and documentation provided by the French authorities contain scientific information, epidemiological data or other evidence that has not been taken into account by the SSC?

Response:

AFSSA did have some additional data to that used by the SSC in its last Opinion on the UK DBES (28 May 1999). The members of the SSC and its TSE/BSE *ad hoc* Group had, likewise, been aware of the recently published scientific evidence that emerged after its Opinion on the UK DBES.

4.2. Question 2

If, in the above documentation, there is new information, data or evidence, or if the SSC has at its disposal any new information, would this require a re-examination of any of the four SSC Opinions directly related to the scientific rationale of the DBES?

Response:

Research on BSE/TSE world wide is extensive and new data is emerging continually. This is reviewed at the monthly meetings of the SSC and its TSE/BSE ad hoc Group.

The questions relating to the usefulness of rapid diagnostic tests for BSE in animals in the pre-clinical stage of the disease were not new since the SSC had dealt explicitly with these issues in its analyses of the BSE tests in clinical cases of BSE as undertaken by the EC and published in Nature in July 1999. The SSC concludes that newly developed diagnostic tests have not as yet been evaluated for their potential usefulness for diagnosing pre-clinical cases of BSE. This evaluation is not a straightforward short-term exercise, but should be given high priority.

Continuing its normal practice of maintaining up-to-date information on BSE, the SSC evaluated all the data provided by the French Authorities. In addition, the SSC obtained further analyses of the epidemiological data on BSE from the UK up to mid-October 1999. These data and a variety of other submissions were evaluated by the TSE/BSE *ad hoc* as well by specifically invited epidemiologists. It is noteworthy that, when strictly comparable data are used, there is clear evidence of the continuing progressive decline in 1999 of BSE in the UK. There is no justification at present to infer any new route of infection. The results of the biological research on the variety of infective agents and their impact on different species highlight further the SSC's original caution in extrapolating from one set of findings, e.g. of the presence of the scrapie agent in organs of experimental animals or sheep to the BSE infectivity of different cattle tissues.

Very recent highly sensitive laboratory assays to detect PrP^{Res}, which have not yet been evaluated extensively, may give grounds for optimism and should be closely monitored. However, these assays are not yet suitable for field use.

The SSC concludes that there are currently no grounds for revising the overall conclusions of the SSC Opinions directly related to the rationale of the DBES.

4.3. Question 3

In the light of the answers to the above question, could the SSC confirm (or not) its position that the conditions of the DBES, if appropriately respected, are satisfactory with regard to the safety of the meat and meat products produced?,

Response:

The SSC emphasises that its analyses of the risk from BSE depend on the Commission and Member States ensuring that proposed measures to exclude or limit the risk are followed meticulously. It notes that the assurance from the UK DBES is very dependent on maintaining the feed ban, the 30-month rule and ensuring that there is clear evidence that the risk from maternal transmission is minimised.

Given these conditions and bearing in mind the SSC's previous analyses of the risk to public health within the EU, the SSC considers that the measures taken by the UK make any risk to human health from the UK DBES at least comparable to that in other European Member States.

Annex 1: **Key elements of the Date-based Export Scheme (DBES)**[10]

The DBES scheme allows the export of

deboned fresh meat from which all adherent tissues, including obvious nervous and lymphatic tissue has been removed, and which is obtained from animals:

- born after the date at which the animal feeding standards (feed ban) were effectively enforced, and
- certified to meet the following conditions:
    - the animal is clearly identified, enabling it to be traced back to the dam and herd of origin; its unique eartag number, date and holding of birth and all movements after birth are recorded either in the animal's official passport or on an official computerised identification and tracing system; the identity of its dam is known;
    - the animal is more than 6 months but less than 30 months of age, determined by reference to an official computer record of its date of birth, or to the animal's official passport;
    - the competent authority has obtained and verified positive evidence that the dam of the animal has lived for at least 6 months after the birth of the eligible animal;
    - the dam of the animal has not developed BSE and is not suspected of having contracted BSE.

If any animal presented for slaughter or any circumstance surrounding its slaughter does not meet all of the requirements, the animal must be automatically rejected

Slaughter of eligible animals must take place in slaughterhouses exclusively used for slaughter of animals under a Date-based Export Scheme or under a Certified Animal Scheme.

The following lymph nodes have to be removed:

> Popliteal, ischiatic, superficial inguinal, deep inguinal, medial and lateral iliac, renal prefemoral, lumbar, costocervical, sternal, prescapular, axilliary and caudal deep cervical.

Meat must be traceable back to the eligible animal, or after cutting, to the animals cut in the same batch, by means of an official tracing system until the time of slaughter. After slaughter, labels must be capable of tracing fresh meat and products back to the eligible animal to enable the consignment concerned to be recalled.

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[10] As annexed to the Opinion of 23 October 1998 of the SSC on The safety of bones produced as by-product of the Date Based Export Scheme.

Annex 2a

NUMBER OF SUSPECT CASES REPORTED BY MONTH OF RESTRICTION AS AT 18/10/99

MONTH	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
JAN		555	1290	2307	4123	4165	3511	2017	1405	536	459	316
FEB		633	1435	1876	3599	3933	3096	1572	1251	501	403	307
MAR		771	1642	2279	4036	4384	3442	1839	1343	521	436	353
APR		639	1257	2510	3829	3639	2729	1482	945	523	384	256
MAY		595	1660	1984	3103	3215	2484	1517	968	447	325	279
JUN	108	637	1271	1831	3237	3104	2313	1334	690	432	334	259
JUL	286	591	1147	2172	3273	3375	2044	1259	775	450	343	224
AUG	356	791	1335	2702	3517	3299	2249	1468	755	454	307	206
SEP	389	722	1425	2848	4034	3617	2203	1314	723	412	324	209
OCT	423	819	1625	3123	4207	3360	2082	1220	762	460	371	84
NOV	447	893	1715	3174	3924	3599	2155	1603	585	427	315	
DEC	503	797	1521	3197	3962	3241	1951	1320	495	441	290	

* Data accumulated to 15 October 1999 *(Excludes private submissions and cases found in surveys)*

Annex 2b

NUMBER OF CONFIRMED CASES REPORTED BY MONTH OF RESTRICTION AS AT 18/10/99

MONTH	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	Pending cases - 1999
JAN		473	1129	1919	3515	3535	2880	1720	1128	445	378	250	
FEB		532	1205	1523	2979	3240	2444	1319	949	409	318	244	
MAR		606	1332	1848	3299	3453	2584	1483	969	392	316	279	1
APR		499	1018	2022	3066	2800	2026	1146	644	406	271	197	2
MAY		439	1259	1572	2323	2329	1814	1146	625	328	215	182	4
JUN	90	529	1010	1494	2544	2313	1787	1039	473	324	213	186	4
JUL	245	506	943	1821	2662	2710	1699	1033	603	331	248	143	19
AUG	310	675	1116	2229	2921	2646	1823	1179	572	343	231	90	78
SEP	335	634	1177	2444	3276	2875	1762	1031	559	295	243	24	169
OCT	365	719	1309	2666	3461	2705	1716	955	587	356	257		
NOV	397	794	1414	2716	3324	3038	1788	1250	485	340	246		
DEC	438	727	1269	2772	3310	2726	1620	1000	419	340	242		
TOTAL	2180	7133	14181	25026	36680	34370	23943	14301	8013	4309	3178	1595	277

* Data accumulated to 15 October 1999 *(Excludes private submissions and cases found in surveys)*

Pending cases are animals placed under restriction for which the outcome is outstanding.

** Please note, that the data previously submitted were as run at the end of September, the usual monthly output. The data for confirmations and pending cases for 1999 have changed in this table because in the intervening period to 15 October, when this table was produced, a further 46 of the cases placed under restriction up to September 30 have now been confirmed. This reduces the number of outstanding cases. The pending total has reduced by more than 46 cases because others will have been negative cases. These changes highlight the fluid nature of the situation depending on the format in which data are requested and presented.

Annex 3: Age at clinical onset of BSE(years) (known age only)

AGE AT CLINICAL ONSET (YEARS) - known age only (as at 1.10.99)

Birth cohort	1-	2-	3-	4-	5-	6-	7-	8-	9-	10-	11-
Pre-1981	0	0	0	0	2	5	47	47	34	32	23
1981/82	0	0	0	0	35	100	106	58	45	17	18
1982/83	0	0	3	120	533	637	331	135	117	58	34
1983/84	0	2	84	903	1861	1254	564	314	136	81	35
1984/85	0	5	343	2160	2801	1572	749	340	189	66	28
1985/86	0	14	675	3554	3916	2510	1079	464	202	73	23
1986/87	0	35	1515	6691	7643	4525	1801	636	209	71	25
1987/88	1	60	3334	13152	12700	6517	2282	699	193	83	21
1988/89	0	19	1061	5121	5635	3014	1125	303	116	44	0
1989/90	0	21	831	3609	3797	1882	598	153	36	0	0
1990/91	1	21	401	1680	1701	765	252	52	0	0	0
1991/92	0	8	402	1469	1312	647	178	0	0	0	0
1992/93	0	6	233	871	1012	464	2	0	0	0	0
1993/94	0	3	117	712	588	11	0	0	0	0	0
1994/95	0	0	106	293	3	0	0	0	0	0	0
1995/96	0	1	18	0	0	0	0	0	0	0	0

The table relates to the cases by age at clinical onset sorted by cohort of birth and age at clinical onset. The totals in this table will differ from the totals in the table in Annex 3, where cases are sorted by year of clinical onset. The reason is that the table sorted by cohort only includes animals with a definite date of birth and a definite date of clinical onset, so that they can be placed in a cohort. The other table includes animals with estimated dates of birth, where for example the farmer is confident of a year of birth, but not month and day. Consequently the latter table will have more cases in than in the present table sorted by cohort.

Annex 4: Age of onset of BSE in animals up to 44 months (Data as at 21.10.99)

	Year of onset														
Age at onset	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1988	1999	Total
20	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
21	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
24	0	0	1	4	2	1	0	0	0	0	0	0	0	0	
25	0	0	0	1	0	0	0	0	0	1	0	0	0	0	
26	0	0	0	1	1	3	1	0	0	0	0	0	0	0	
27	0	0	1	1	3	3	2	0	0	0	0	0	0	0	
28	0	0	1	3	1	1	3	0	0	0	0	0	0	0	
29	0	0	0	2	3	2	3	1	0	0	1	0	0	0	
30	1	1	2	5	10	4	3	3	2	0	1	0	0	0	
31	0	1	0	8	6	5	0	1	2	0	0	0	0	0	
32	0	1	4	6	6	5	3	4	1	1	0	0	0	0	
33	1	0	4	3	9	13	6	1	2	0	2	0	0	0	
34	0	0	4	3	11	10	9	4	2	2	1	0	1	0	
35	1	1	7	6	27	17	8	4	5	8	1	0	0	0	
36	0	2	15	46	134	39	17	7	7	1	6	0	1	0	
37	0	6	8	20	58	51	19	9	5	8	2	7	2	0	
38	0	3	13	25	99	70	33	12	14	9	5	3	2	0	
39	0	3	9	30	116	163	36	26	17	17	9	5	0	2	
40	0	6	17	42	105	224	64	42	18	26	19	4	10	0	
41	0	6	20	42	129	243	74	56	33	28	15	8	6	1	
42	0	8	29	69	161	377	99	78	34	37	24	6	19	2	
43	1	6	42	61	191	433	127	94	52	46	30	13	12	3	
44	0	10	54	87	192	461	163	122	61	55	33	14	22	7	
Under 31	1	1	5	18	20	14	13	4	2	1	2	0	0	0	81
Under 34	2	3	13	35	41	37	22	10	7	2	4	0	0	0	
Under 36	3	4	24	44	79	64	39	18	14	12	6	0	1	0	308
Under 38	3	12	47	110	271	154	75	34	26	21	14	7	4	0	778
Under 41	3	24	86	207	591	611	208	114	75	73	47	19	16	2	2076
Under 45	4	54	231	466	1264	2125	671	464	255	239	149	60	75	15	6072
Total cases	12	460	3139	7775	14610	25862	37146	33770	22912	13818	7426	4241	3099	1416	175686
% Under 31	8,33	0,22	0,16	0,23	0,14	0,05	0,03	0,01	0,01	0,01	0,03	0,00	0,00	0,00	
% Under 34	16,67	0,65	0,41	0,45	0,28	0,14	0,06	0,03	0,03	0,01	0,05	0,00	0,00	0,00	
% Under 36	25,00	0,87	0,76	0,57	0,54	0,25	0,10	0,05	0,06	0,09	0,08	0,00	0,03	0,00	0,175312
% Under 38	25,00	2,61	1,50	1,41	1,85	0,60	0,20	0,10	0,11	0,15	0,19	0,17	0,13	0,00	
% Under 41	25,00	5,22	2,74	2,66	4,05	2,36	0,56	0,34	0,33	0,53	0,63	0,45	0,52	0,14	
% Under 45	33,33	11,74	7,36	5,99	8,65	8,22	1,81	1,37	1,11	1,73	2,01	1,41	2,42	1,06	

Under 36 month cases represent 0.175% **or 308** of all confirmed cases, o**ut of which approx. 50% were born before any measure was taken and none was borne after August 1996.** The table uses estimated ages and best estimates of clinical onset.

Annex 5: Numbers of confirmed BSE Cases[1] (status: 27.10.99)

country	>1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999[2]	Total[2]	%
UK	442	2473	7166	14294	25202	37056	34829	24290	14473	8091	4334	3197	1600	177447(4)	98,66
Ilse of Man	-	6	6	22	67	109	111	55	33	11	9	5		435	
Jersey	-	1	4	8	15	23	35	22	10	12	5	6	1	144	
Guernsey	4	34	52	83	75	92	115	69	44	36	43	24		676	
Falkland	-	-	1*	-	-	-	-	-	-	-	-	-	3	1*	
													5		
													-		
(UK)	446	2514	7229	14407	25359	37281	35090	24436	14560	8150	4391	3232	1609	178703	99,36
B	-	-	-	-	-	-	-	-	-	-	1	6		9	-
DK	-	-	-	-	-	1*	-	-	-	-	-	-	2	1*	-
D	-	-	-	-	-	1*	-	3*	-	-	2*	-		6*	-
F	-	-	-	-	5	-	1	4	3	12	6	18	-	71	0,04
IRL	-	-	15**	14**	17**	18**	16	19**	16**	73	78	79		410	0,23
I	-	-	-	-	-	-	-	2*	-	-	-	-	22	2*	-
L	-	-	-	-	-	-	-	-	-	-	1	-		1	-
NL	-	-	-	-	-	-	-	-	-	-	2	2	65	6	-
P	-	-	-	1*	1*	1*	3*	12	14	29	30	106		330	0,18
													-		
													-		
													2		
													133		
UE (except UK)	-	_	15	15	23	21	20	40	33	114	120	211	224	836	0,46
CH	-	-	-	2	8	15	29	64	68	45	38	14		315	0,18
Others[3]:	-	-	2*	-	-	-	1*	-	-	-	-	2	32	5	-
													-		
Total (excl. UK)	-	-	17	17	31	36	50	104	101	159	158	227	256	1156	0,64
Total (world)	446	2514	7246	14424	25390	37316	35140	24540	14661	8309	4549	3459	1865	179859	100%

(*): imported animals

(**): Ireland: Includes the imported cases (5 in 1989, 1 in 1990, 2 in 1991 and 1992, 1 in 1994 and 1995)
(1): Sources: European Commission; OIE; MAFF (UK)
(2): Provisory figures. Dates of confirmation of the latest cases: Belgium (28 June), France (25 October), Ireland (21 October), The Netherlands (17 March), Portugal (11 October), Switzerland (17 September), UK (18 October 1999)
(3) 1989 (Oman: 2) - 1993 (Canada: 1) – 1998 (Liechtenstein: 2)