EUROPEAN COMMISSION
DIRECTORATE-GENERAL XXIV
CONSUMER POLICY AND CONSUMER HEALTH PROTECTION
Directorate B - Scientific Health Opinions
Unit B1 - Monitoring and dissemination of scientific opinions

SUMMARY REPORT BASED ON THE MEETINGS OF 14 AND 25 OCTOBER 1999 OF THE TSE/BSE *AD-HOC* GROUP 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 AND EDITED FOLLOWING A WRITTEN PROCEDURE (26.10-16.11.99)

Summary Report based on the meetings of 14 and 25 October 1999 of the TSE/BSE *ad-hoc* group of the Scientific Steering Committee

Preliminary remark:

The present document was adopted following several cycles of written consultation by e-mail, between 26 October and 15 November 1999.

Participants, meeting of 14 October 1999:

Prof.V.Silano (chairing the meeting), Prof.M.Gibney, Dr.S.Gore, Dr.D.Heim. Prof.H.Kretzschmar, Prof.H.Budka, Prof.M.Vanbelle, Dr.E.Vanopdenbosch, Dr.P.Verger, Prof.D.Dormont, Dr.J.Schlatter. Prof.P.James[1]

C.Berlingieri, J.Kreysa, I.Peutz, D.Jacquemin, P.Vossen (Commission)

Apologies were received from: Prof.G.Piva, Prof.A.Osterhaus, Prof.A.Aguzzi.

Participants, meeting of 25 October 1999:

Prof.V.Silano (chairing the meeting), Dr.S.Gore, Dr.D.Heim. Prof.H.Kretzschmar, Prof.H.Budka, Prof.M.Vanbelle, Dr.E.Vanopdenbosch, Dr.P.Verger, Prof.D.Dormont, Dr.J.Schlatter.

Apologies were received from: Prof.M.Gibney, Prof.A.Osterhaus, Prof.G.Piva, Prof.A.Aguzzi, Prof.P.James

C.Berlingieri, K.Hakulin, G.Morrsion, P.Vossen. (Commission)

The following experts also attended the meeting as observers: Dr.D.Matthews, Dr.J.Wilesmith, Prof. M.Eloit, Dr. A.Alperovitch. Their role was confined to the provision of information, data or clarifications when requested. They did not participate in the discussions as such of the *ad hoc* Group and left the room at the time of the final deliberations.

1. **Chairman** of the meetings was Prof. V.Silano, member of the TSE/BSE ad hoc Group and vice chairman of the Scientific Steering Committee. He replaced Prof.Gibney, who attended but did not chair the first meeting for practical reasons.

2. **Declarations of interest.**

As foreseen in the Rules of Procedures of the Scientific Steering Committee and its Working Groups, the participants were requested whether any of them had a possible conflict of interest to declare. The participants were unanimous that they were members of the TSE/BSE *ad hoc* Group in their capacity of scientist, that they did not represent any Government or other body.

The Commission services pointed out that the concept "interest" had to be understood as including the notion of "intellectual interest". The position of one of

[1] Prof.James had to combine this meeting with another priority Commission meeting and was present during parts of the morning and afternoon sessions.

the members of the *ad hoc* Group who chaired an expert group that adopted a scientific opinion that is divergent from the SSC opinions was discussed by the members of the *ad hoc* Group and evaluated in the light of a potential conflict of interest. After discussion, the Chairperson, together with the other members of the TSE/BSE *ad hoc* Group considered that all the members of the ad hoc Group were able to act independently and in consequence to participate in the discussions.

3. Further procedural matters.

a. The participants agreed to focus on truly scientific matters and to keep the outcome of the meeting confidential as it was only a preliminary stage of the procedure which enables the SSC to eventually formulate an opinion.

b. Documents needed for the meetings had been provided to all participants before the meeting, as soon as available. However, documents that only became available the day before or just before the meeting, were distributed at the beginning of the meeting. At the beginning of each meeting, the Secretariat made an account of all the documents that should be available to all participants. The observers received the documents needed for the second meeting, except the draft minutes of the meeting of 14 October.

c. The secretariat was requested by all participants to produce this report on the meetings and to submit it for written consultation to the TSE/BSE ad hoc Group members.

4. Discussion of the Opinion of 30 September 1999 of the French Group of Experts on Sub-acute Spongiform Transmissible Encephalopathies.

4.1. Background

Following the contrary advice emitted on 30 September 1999 by the recently established French Food Safety Agency (the *Agence Française de Sécurité Sanitaire des Aliments,* AFSSA) with respect to the "*draft decree modifying the decree of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom"*, the Commission submitted 3 questions to the Scientific Steering Committee:

1. Are the opinions and documentation provided by the French authorities containing scientific information, epidemiological data or other evidence which has not been taken into account by the SSC?
2. If there is in the above documentation new information, data or evidence, or if you have at your disposal any such new information, would this ask for a re-examination of any the 4 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 produced meat and meat-products?

These questions were discussed by the TSE/BSE *ad hoc* Group at two meetings (14 and 25 October). A draft report based on these meetings was prepared which

served as basis for the discussions of the Scientific Steering Committee at its meeting of 28-29 October 1999.

The AFSSA advice is based on the Opinion of 30 September 1999 of the French Group of Experts on Transmissible Sub-acute Spongiform Encephalopathies (previously the Inter-ministerial Committee on Transmissible Sub-acute Spongiform Encephalopathies, established in April 1996) regarding the lifting of the UK Export ban. In addition, this expert group adopted on 1 July 1999 an opinion on the BSE Epidemic in the UK. A copy of these 3 documents has been provided to all members, as well as their translation into English.

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, can be summarised as follows:

a) The upcoming indication that much more sensitive tests are emerging which could allow finding PRP^{Sc} in tissues in which so far no infectivity has been detected by heterologous bioassay[2].

b) The similarity of the number of confirmed cases reported in UK in the period January to end of August 1998 and 1999[3], suggesting 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 programs (i.e., in the UK: brain histopathology of bovines slaughtered under the OTMS[4]; in Switzerland: the Prionics test, all positives confirmed by histology or immuncytochemistry, on all adult cows in fallen stock, emergency slaughters and a sample of routinely slaughtered adult cows)[5].

e) Doubts on the traceability of meat products.

When preparing their opinions, the French Group of Experts discussed these points purely scientifically and did not take into account the FVO-reports. They took due account of the SSC's opinions on the DBES of 1997 and 1998, of additional scientific information that had become available since the SSC's latest opinion of 28 May 1999 on *Monitoring some important aspects of the evolution*

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2 It is important to signal the difference between heterologous and autologous bioassays, as the levels of detection measurable by heterologous bioassays (between bovine and rodent, for example) are significantly lower to those measured by autologous assays. The negativity of a cattle-to-cattle transmission will require at least 6 to 8 years of observations on one hand and, on the other hand, the large majority of the infectivity assays on organs and tissues was evaluated by heterologous essays.

3 According to the UK report *BSE: Measures taken by the UK – Report for the month to the end of August 1999*, the number of suspected BSE cases in Great Britain up to 31 August and placed under restriction was: 2199 in 1999 and 2991 in 1998. Of these, BSE was confirmed on 31 August in 1320 cattle in 1999 and 1379 in 1998.

4 Samples of both caudal and rostral medulla are being tested by westren blot.

5 The potential of applying the recently evaluated rapid diagnostic BSE-tests and of new analytical possibilities such as mentioned under a), for surveillance and monitoring of TSEs to representative samplings ["sondages"] or in pilot studies on so called "risk populations" are further discussed in sections 4.4 and 5.

of the epidemic of BSE in Great Britain (Status: April 1999) and of epidemiological data that became available after 28.05.99.

The following 4 points were discussed by the *ad hoc* Group.

a) The possibility to verify the distribution of PRP^{Sc} in the various body tissues and fluids of infected (incubating) cattle and linked to this the question of the 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 new transmission routes.
c) The potential of the recently evaluated rapid diagnostic BSE-tests and of new analytical possibilities with regard to surveillance and monitoring of TSEs.
d) The traceability of the meat and meat-derived products.

4.2. Distribution of infectivity in the tissues of infected animals

Consensus was reached that experiments with scrapie-infected sheep indicate that more sensitive laboratory methods are now available which are potentially able to confirm the presence of PrP^{Sc} in much lower concentrations than before. Using these methods could allow finding PrP^{Sc} in other tissues than those presently known to carry infectivity by extensive heterologous bioassay. Schmerr *et al* (1999)[6] found PrP^{Sc} in blood of scrapie infected sheep and hamster and of CWD infected elk before the onset of clinical signs. Preliminary and still unpublished French research results also indicate the presence of PrP^{Sc} in infected tonsils of genetically susceptible lambs as soon as 1 months after birth to a scrapie infected ewe (Prof.Dormont, oral communication). The presence of PrP^{Sc} in tonsils and the appendix of vCJD patients has been reported in advance of disease onset (8 months for the appendix). Moreover, results of a recently completed study on the pathogenesis of scrapie and BSE in mice after oral inoculation clearly demonstrate widespread involvement of the lymphoid system in both models (Maignien *et al*, 1999)[7]. Thus, in BSE and scrapie mouse models, the involvement of pereipheral lymphoid tissue is quite clear.

Consensus was reached on the difficulty of and the many uncertainties linked to, extrapolating from scrapie data on organ spread to BSE in view of emerging evidence that the pathogenesis of different TSEs is rather different. Maingien *et al* (1999) showed that genetically identical mice, orally challenged with BSE or scrapie, showed different distribution of the infectivity throughout their bodies. Other recent research supports the hypothesis of different pathogenic pathways in sheep and bovines (for example the absence of BSE infectivity in the spleen of BSE clinically affected cattle, but presence of scrapie infectivity in the spleen of scrapie sheep; the presence of infectivity in the spleen of sheep experimentally infected with BSE).

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6 **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.

7 **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, 80, 3035-3042.

A discussion was also held on the new analytical method developed by Schmerr *et al* and reported in the Tübingen seminar (September 1999)[8] and recently published in two peer-reviewed journals. M.J.Schmerr had presented her data already at a WHO meeting in Geneva in March 1999. The potential utility of this assay was recognised in the report of this meeting (WHO, June 1999). As far as the validity of the Schmerr *et al* method is concerned, there was general agreement that this is an interesting development but that the scientific evidence of its applicability/functionality is not yet clearly assessed. For example, a double blind validation study would need to be done.

The work of Kretzschmar and Eigen (see: Tübingen Conference Notes, September 1999) was also mentioned, showing the potential to detect as low as one i/c infective unit of human CJD prions and possibly less. Titration in mice is ongoing to verify the sensitivity of this rather complicated method. The point made was that new, ever more sensitive tests are constantly emerging and that eventually tests identifying single PrP aggregates may become available. But the question was raised in how far this would be relevant with respect to the infectivity of bovine tissues containing very low concentrations of PrP^{Sc} for animals and, in particular, for man.

It was generally agreed that the presence of PrP^{Sc} at levels above the detection limit can be taken as indicator of the development of the disease (on the basis that clinical disease is certain if the individual lives long enough). Current detection levels relate to such large aggregates of PrP^{Sc} that one should accept that replication after challenge has taken place. Furthermore the absence of PrP^{Sc} in currently detectable concentrations does not necessarily guarantee its absence.[9]

It was also agreed that also other constantly improving laboratory methods should be used to better understand the distribution of PrP^{Sc} in the body of infected (pre-clinical) animals, particularly with respect to BSE in cattle.[10]

From the discussion a general debate on the usefulness of the recently evaluated *post-mortem* BSE tests for surveillance emerged. It was also agreed that other constantly improving laboratory methods should be used to better understand the distribution of PrP^{Sc} in the body of infected (pre-clinical) animals, particularly with respect to BSE.[11]

With regard to the relevance of the new scientific information on testing for infectivity with respect to the DBES, 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 of the still ongoing pathogenesis

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8 **Conference notes.** Characterisation and Diagnosis of Prion Diseases in Animals and Man. Tübingen, 23-25 September 1999.

9 The TSE/BSE ad hoc Group is aware of this critical point and therefore installed the Working Group "Human Exposure Limit Line".

10 A working Group on the *Safety of ruminant blood* has recently been installed by the SSC. (See SSC minutes of 16-17 September 1999.

11 A working Group on the *Safety of ruminant blood* has recently been installed by the SSC. (See SSC minutes of 16-17 September 1999.

experiment. This experiment [12,13] started in April 1992 and is based on oral cattle-to-cattle transmission with 100 grams of contaminated macerated 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 already known (in 1998) not to harbour 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 clinical disease 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 post inoculation. 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, 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, without clinical disease.

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, these experimental data with intra-cerebral challenge and an incubation period of 6½ years are strongly suggestive of no or very low 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.

It was therefore agreed that:

- at present, although bioassay from cattle-to-cattle are still ongoing, there is no experimental evidence (by the most sensitive biological assay system of cattle-to-cattle transmission), that meat of pre-clinical BSE-cases can transmit BSE but the question will still be pending from the experimental point of view for

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

13 **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.

several years. Deboned meat, if properly deboned, is therefore very unlikely to carry an infection risk for humans.[14]

- Ideally, no BSE infected animals should enter the food chain, anywhere in the world. In practice, because of the absence of tests routinely applicable for detecting (pre-clinical) infected cases, the probability of animals being infected should also be taken into account. Even if the risk for man carried by the meat of an infected animal is negligible on the basis of cattle tests, it is clear that the meat of confirmed BSE-cases and of animals at risk[15] should not be allowed to enter the food chain, also because of the risk of cross-contamination with tissues found to be infective.
- However, the risk of cross-contamination exists for (pre-)clinical cases. Therefore, cross-contamination should be avoided by all means[16] if the risk of BSE infection cannot be excluded.

Note: The *ad hoc* Group paid also attention to the recent publication of Anil et al (1999) [17], pointing at the risks of contamination of blood with CNS tissue resulting from certain slaughter methods. The Group referred to the opinions of the SSC of 9 December 1997 (Specified Risk Materials[18]) and of 25 June 1999 (Fallen stock) and to the opinion of the Scientific Committee for Veterinary Measures relating to Public Health of 17 February 1998 on *The use of pneumatic stunning with air injection*, which deal with this issue. The *ad hoc* Group recommends that the SSC verifies whether these opinions need to be amended.[19]

4.3. Epidemiology and transmission.

a. An apparent discrepancy in the epidemiological data on which the position of the French experts is based could not be resolved by information on the most recent BSE data from the UK available to the ad hoc Group at its meeting of 14 October

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[14] However, evolution in this field should be closely and permanently monitored as some earlier assumptions in the history of BSE have later turned out to be wrong (e.g., prior to 1996, there were also no indications that BSE could be transmissible to humans).

[15] "At risk is defined as follows in the SSC's Fallen Stock Opinion (June 1999):] "Animals or materials *at (TSE) risk* are those not showing clinical signs but where the risk of being infected is definite, for example animals that, after epidemiological investigation, were found to have been exposed to a common source of infection with a confirmed TSE case (for example feed) and including the progeny of TSE cases." Some members suggested that the definition should also include the risk is associated with animals from herds in which cases of BSE have been diagnosed.

[16] For example, by the use of dedicated slaughter and processing lines, removal of specified risk materials, etc.

[17] Anil *et al*, 1999. Potential contamination of beef carcasses with brain tissue at slaughter. Vet.Rec., 145, 460-462

[18] It is noted that Commission Decision 97/534/EC (on specified risk materials) is still not in force, although several member states do already remove SRMs.

[19] In relation to pithing of cattle, it is mentioned that the abattoir currently approved for DBES does not pith. However, the methods currently used in the EU, including in the UK, should, also in the light of the above Anil *et al* (1999) study be evaluated for their capacity to induce brain tissue dissemination in blood, especially in high risk countries.

1999. The required data were made available by SEAC, the UK Spongiform Encephalopathy Advisory Committee, after the meeting. They were discussed on 22 October by a group of 4 epidemiologists whose report was provided to the TSE/BSE *ad hoc* Group on 25 October 1999. The data compare the developments in 1998 and 1999 on a monthly basis, up to mid October 1999. They are attached as Annexes 1a and 1b.

The relevance of the assumed development of the epidemic in the entire UK-cattle herd for the sub-population falling under the DBES was discussed in detail.

The TSE/BSE ad hoc Group concluded that the decreasing trend of the number of BSE cases is confirmed, be it that the post-1996 decrease is less sharp[20] than for the pairs of years 1994/1993, 1995/1994, 1996/1995 and 1997/1996. (See also Annex 2). However, the present number of BSE cases is within the upper limits of confidence of model predictions.

The *ad hoc* Group mentioned that predictions based on models have their limits, as they depend upon the assumptions made, imperfections in the models, etc. (See also the SSC opinion of 28 May 1999 on the Evolution of the BSE epidemic in Great Britain.) Several members of the ad hoc Group were of the opinion that given these uncertainties, decisions concerning public health should be taken on the basis of actual data rather than predictions.

The levelling-off of the rate of decrease of the BSE incidence in the tail end of the epidemic could indicate the appearance of a new factor that was previously hidden by the overwhelming effect of the feed factor and by the maternal transmission factor. Such an hypothetical factor could be valid also for the animals born after 1/8/96. (As matter of fact, some time indeed elapsed before statistical evidence of maternal transmission could be shown.) A continued decline of the incidence as shown by birth cohorts 1992/93, 1993/94, 1994/95, etc. would be seen as reassuring. As to other transmission routes than oral (feed) or maternal transmission, an otherwise not explainable slow-down of the rate of decrease in the development of the epidemic could potentially be explained by assuming a hitherto unknown transmission route.

The participants agreed that at present no scientific evidence is available pointing towards the existence of other routes of transmission than through contaminated feed or via maternal transmission[21]. However, such third mechanism cannot be excluded a priori. Several possible reasons to explain the slower decrease, were mentioned, specifically:

- Although it is recognised that the 1988 feed ban was not 100% effective, it resulted in a drastic decrease of BSE after a period equal to the average incubation period. This has rapidly reduced the highest number of cases

[20] The decline in the first 6 months of 1999 (for which practically complete figures are available) of confirmed BSE cases [these figures do not take into account the effects of changes in the age distribution of the British herd over recent years] was the slowest since 1993 when data for the first 6 months of subsequent years are compared.

[21] Maternal transmission was judged not to influence significantly the epidemic. Most, but not all members also considered that the third hypothetical mechanism will most probably, if existing, influence the epidemic even less.

resulting from direct feed contamination (prior to 1988) and avoided a further exponential growth of the infections epidemic.

- However, it is also recognised that after 1988 feed was consumed that was contaminated either by cross-contamination or by inappropriate farming practices. The infective load of such feed was the highest in the years 1991-1994, when the prevalence of late infections was at its highest. Animals born before the real ban of 1 August 1996 would then have been exposed to the highest infective loads in (cross-contaminated) feedstuffs resulting in the present slow-down.
- The various risk reduction measures implemented since 1988 have not necessarily all had the same quantitative effect, they may have been implemented gradually and the effect does not necessarily become apparent exactly after a number of years equal to the mean incubation period (See Donnelly and Ferguson, 1999). For example, the effects of the August 1995 UK measure to tighten the regulation on specified risk materials (the whole head was included in the SRM list, previously only the brain, resulting in a possibly contaminated skull), were only just becoming apparent in 1999 by observing the decline of the number of BSE cases at age 3-4 years from the 1995/1996 birth cohort.
- A third possible mechanism of disease transmission. Such mechanism would only become apparent after elimination of the effect of contaminated feed and maternal transmission, which may have masked it. Although it can not be excluded a priori that its importance may increase over time, it is estimated from the present evolution of the epidemic, which is consistent within the predictions, that the present contribution of such mechanism, if existing, would be minor as compared to the presently known routes.

b. The group questioned the relevance of a possible reduced rate of decline of the epidemic in the DBES context because the current BSE incidence figures would relate to the infectivity-situation before December 1995 (so far there are no cases born after December 1995, and so none after the real ban of 1 August 1996). The risk of becoming infected via contaminated feed changed significantly during 1996 and is considered to be effectively eliminated since 1/8/96 when the MBM ban was finally enforced and audited by field surveys and all stocks confiscated. Extrapolating from pre-1996 birth cohorts to post-1996 cohorts therefore seems to be inappropriate. Nevertheless, if the implementation of the MBM ban in August 1996 is not properly done, the reverse should be considered.

   However, no final conclusion was reached as to the relevance of the development of the UK epidemic for the probability that DBES-animals could be infected. More epidemiological data and calculations are needed to conclude on this point. However the original scheme for specifying risks in Britain was considered by the SSC in February 1998 on the basis of the risk analysis submitted by the UK Ministry of Agriculture, Food and Fisheries (MAFF) requested in the SSC opinion of December 1997 and additional recommendations were made.

   The ad hoc Group agreed with the statement in the SSC opinion of 28.05.99 that, given the fact that at present BSE can only be diagnosed at the end of the incubation period, the effectiveness of the additional SRM measures (see above)

of August 1995 and of the August 1996-feed-ban can only be finally assessed in 2000 and 2001, respectively, or later.

c. The application of the recently evaluated post-mortem BSE tests in all countries, according to protocols similar to the ones applied in Switzerland and the UK, was discussed. The *ad hoc* Group agreed that the application of the new BSE-tests on the basis of an approach similar to the one applied in Switzerland would be useful for better estimating the prevalence of BSE cases in the late 1990s, not only in UK but in all Member States, and for estimating incidence of BSE infection in bovines born after 1 August 1996 in the UK. [Suggestion for UK: testing of OTMS cattle would be important; survey results should be made available by year of birth of bovines tested and specifically by whether born before or after 1 August 1996]. It was agreed that the application conditions and criteria of the tests in a similar way in other Member States should be further examined.

   The ad hoc Group also agreed that case-control studies should be carried out if BSE cases were born after 1 August 1996, in order to be able to understand the risk factors associated and to check their relevance to known contamination mechanisms.

d. The usefulness of applying such tests to DBES-animals (age: 6-30 months) was discussed and a conclusion reached that even for the oldest age class in the DBES scheme (for example 24-30 months, where the likelihood to find infection, if any, would be the highest), the entire population may have to be tested in order to potentially provide statistically significant and reliable results, if any.

   In this context a discussion was held along the following-lines:

   - Given that the most sensitive tests seem to be able to detect infectivity in brain and spinal cord in the last few months of the incubation period, it may be useful to apply them to a sample of the oldest available animals born after 1 August 1996 and slaughtered in the OTMS that otherwise comply with the DBES criteria. (See annex 3 for an estimate of the number of possible cases that would be involved.) Verifying the presence of PrP^{Sc} at levels above the detection limit, which would be assumed to equate to late incubation in a representative sample[22] of DBES animals of approximately 40 months, would therefore increase the confidence in the safety of the meat from DBES exported animals.

   - The possible application of rapid *post mortem* diagnostic tests in UK cattle born after 1 August 1996, but presently older then 30 months, was discussed. However, *assuming a priori* a low infection incidence, a very large number of DBES bovines would have to be tested for 'nil positives' to be genuinely informative about infection incidence. Information may come sooner from clinical BSE cases (if any) in bovines born after 1 August 1996. Nevertheless, positive results would be of great value.

[22] It is assumed that animals of the DBE Scheme are normally grass-reared animals and in these animals the risk of being infected is less. For doing a survey, such animals are not the best target. This assumption, according to other members, would need to be verified especially for the first year of life of the animals.

- The practicability of the previous proposal would need to be assessed because: (1) although there are strong indications that tests would pick-up PrP^{Sc} in the CNS prior to clinical disease onset, the applicability of the test on pre-clinical animals still needs to be verified; (2) the probability to find an animal that is infected is low and the test would therefore need to be applied to a very high number (if not: all) animals. Testing animals of approx. 40 months that otherwise comply with the DBES would therefore not be a matter of routine that can be carried out within a few weeks but may well appear to be a major exercise taking many months; (3) given the large number required and the fact that the tests are not yet validated for pre-clinical stages, they may provide a non-justified impression of safety or danger if false negatives and/or false positives were found. It was agreed that the statistical credentials for such programme would need to be worked out, as well as its feasibility.

4.4. The new BSE-tests[23]

The new BSE-tests were discussed in much detail in the context of the two previous issues and it was concluded that:

- This is a new tool which should be used in research (detection of PrP^{Sc} in CNS tissues as a function of the stage of advancement of the incubation period) and, as widely and as soon as reasonably possible, in surveillance and in monitoring (target risk populations). An in-depth scientific assessment of their applicability (sensitivity, sample size required, interpretation of results,…) to target populations (certain age classes, fallen stock, emergency slaughters, ….) other than clinically diseased animals would therefore be appropriate.
- The potential and the possibility of applying the recently evaluated rapid diagnostic BSE-tests and of new analytical possibilities with regard to surveillance and monitoring of TSEs to representative samplings ["sondages"] or in pilot studies on so called "risk populations" should be assessed. Risk groups are (see also the recent Swiss and UK surveillance programme updates) fallen stock and emergency slaughters. In the UK, the potential and possibility of a survey on a statistically justified sample of the oldest available age section of animals born after 1 August 1996 that otherwise comply with the DBES criteria, should also been envisaged.

4.5. Traceability of meat products

The *ad-hoc* Group agreed that the existence of an effective and safe system for identification and tracing is of crucial importance, particularly for meat-derived products and that, if not already implemented, it's putting into place would need several months. But this was considered to be a control problem and not a scientific issue. The ad hoc group 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). Rigorous controls are in place to ensure the origin and backtracing

[23] The secretariat informed the ad-hoc group that the Commission is currently preparing an exercise where the tests shall be applied to different tissues of animals known to be in different stages of incubation. The UK has promised to provide the material.

of the meat. The Commission further informed that a control mission of April 1999 did not find any problems that would endanger the compliance with the DBES criteria. A new control mission took place in early October and the results are awaited.

5. Further discussion

The TSE/BSE *ad hoc* Group concluded its meetings by an exchange on the 3 questions submitted by the Commission to the SSC.

On Question 1, *whether the opinions and documentation provided by the French authorities containing scientific information, epidemiological data or other evidence which has not been taken into account by the SSC*, there was a general agreement that the more sensitive laboratory techniques to detect PrP^{Sc} in tissues that had recently become available, needed to be monitored closely. They may indeed eventually lead to the identification of PrP^{Sc} and accordingly TSE agent[24] in tissues where so far no infectivity had been detected with the most sensitive assays available until now. Also the reports on the detection of scrapie agent in sheep blood, although the technique needs further validation, confirms previous hypothesis on the pathogenesis of TSE in sheep. Whether this can be extrapolated to BSE in cattle and whether presence at very low titers of a TSE agent equals a tissue to be infectious, needs further research. So far, there is no evidence of bovine blood or meat to be infectious and the results so far of the cattle-to-cattle pathogenesis study point against this but, on the other hand, the most recent and sensitive results are still awaited (experiments are in progress). Furthermore, cross-contamination of meat and meat products with potentially infected tissues needs to be avoided by all means.

On questions 2 and 3, whether *a re-examination of any of the 4 SSC opinions directly related to the scientific rationale of the DBES was desirable* and whether *the conditions of the DBES, if appropriately respected, are satisfactory with regard to the safety of the produced meat and meat-products*, the TSE/BSE *ad hoc* Group shared the general orientation in all the SSC opinions, that the certainty that a product contains a zero risk level can presently not be achieved for any bovine derived product in a country where native BSE cannot be excluded be it at high or low incidence levels, although overall incidence has to be taken into account in risk assessment.

The way(s) how to deal with this fact should be seen from a public health angle of view, and elements such as the BSE incidence, the factors that contribute to the geographical BSE risk of a country or region (e.g., the evolution over time of its incidence, the measures taken to mitigate the BSE agent propagation risk), the intended end-use and numbers of humans that would be consuming meat or meat derived products from a possibly infected animal if any, should be taken into account.

However, the TSE/BSE ad hoc Group did not come to an unanimous conclusions as to how to deal with questions 2 and 3.

[24] The new tests currently detect PrP^{Sc} which is generally considered as a surrogate marker for infectivity.

On one hand, accepting the fact that a complete zero risk is impossible to achieve in countries where BSE cannot be excluded, one can justify that the SSC's 4 opinions related to the DBES do not need to be re-analysed because the residual risk would be remote and DBES animals should not be considered to be at risk, for the following reasons: properly deboned meat is according to present knowledge unlikely to carry an infection risk for humans, the epidemic is further decreasing within the scientifically expected boundaries, the number of animals possibly infected by maternal transmission would be very small, these animals would be below 30 months, the SRMs and certain other tissues would be removed, they would have never been fed possibly contaminated feed and there is the guarantee that their dam would have survived for at least 6 months without developing BSE, resulting in a significant mitigation of the risk of maternal transmission. However, along with the implementation of the DBES, the implementation of programs may be envisaged such as (1) research on TSE infectivity, (2) verification of the recently evaluated *post-mortem* diagnostic tests for their capacity to detect infectivity in earlier stages of incubation and (3) the launching of targeted sampling program in order to try to identify infected animals in high risk populations (fallen stock; emergency slaughters), and in the older sections of animals born after July 96 that otherwise comply with the DBES criteria and (4) further continuous monitoring of the evolution of the epidemic, especially with regard to BSE cases born after the real feed ban of 1 August 1996. The occurrence of such cases should be carefully evaluated as they may point at an exposure to a source of infection other then feed or maternal transmission. This risk would be higher in farms where more then 1 case occurs.

On the other hand, one can consider on the contrary that a reassessment of the validity of the DBES-related SSC opinions, and possibly of the risk of consumption of deboned meat from all countries with native BSE cases, will be necessary in 12 (possibly 24) months from now and that it would be useful to postpone the decisions by then, because at that moment it would be possible to take into account:

- possible new results from more sensitive laboratory tests on possible presence of TSE agent[24] in tissues where no infectivity has been detected so far by mouse bioassay;
- the results of targeted surveys on risk groups within the cattle herds (fallen stock, emergency slaughter, OTMS animals) and on the oldest animals that otherwise comply with the DBES criteria;
- the results of a close monitoring of the further evolution of the BSE epidemic in the UK, in the light of the possible existence of a third mechanisms of BSE transmission or a non complete compliance with the feed ban; the results can be assessed one mean incubation time in cattle (or 4 to 5 years at the earliest) after August 1996.
- the results of the validation studies to asses whether the recently evaluated post-mortem diagnostic tests have the potential indeed to detect the presence of the agent[24] in earlier stages of the incubation period;

- the outcome of the SSC Working Group on "culling", which will assess[25]. whether culling the complete herd if one BSE case occurred, is an appropriate measure to control BSE epidemics. Meanwhile, as a precautionary measure, farms where BSE has occurred after August 1996 should be excluded from the DBES, including if the BSE cases were born before August 1996, to avoid the risks resulting from failures in the feed ban and from the possible 3rd mechanism of transmission.

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[25] e.g., including back calculation for 1990-1994 and prospective calculation for 1999-2002 period.

Annex 1a

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 1b

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 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 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 2: Age at clinical onset of BSE as at 01/10/99 (years) (known age only)

AGE AT CLINICAL ONSET (YEARS) - known age only

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

This 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 (Annex 3) will have more cases in than in the present table (Annex 2) sorted by cohort.

Annex 3: 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.