



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Draft minutes of the 80th meeting held on 26th November 2003

At

Church House Conference Centre
Dean's Yard
Westminster
London

Members:

Professor P. Smith (Chairman)
Professor A. Aguzzi
Professor R. Anderson
Professor C. Bostock
Professor G. Bulfield
Professor R. Carrell
Mr P. Jinman
Professor H. Kimbell
Professor C. Masters
Professor I. McConnell

Technical Advisors:

Dr P. Barrowman (Defra)
Dr S. Dixon (FSA)
Mr P. Soul (Defra)
Dr J. Stephenson (DH)
Dr D. Matthews (VLA)

Assessors:

Mr A. Harvey (FSA)
Dr R. Jecock (DH)

SEAC Secretary:

Dr C. Boyle

Observers:

Dr Y. Boyd (Defra)
Dr G. Cadwallader (MRC)
Dr P. Christie (SE)
Dr P. Crook (EA)
Dr A. Douglas (DARDNI)
Dr I. Hill (FSA)
Dr M. Simmons (NAWAD)
Dr H. Tyson (BBSRC)

Secretariat:

Mr M. Pemberton
Dr B. Jeffery
Dr P. Keep
Dr C. Ravirajan
Ms T. Dale

Also in attendance:

Mr D. Carruthers (Paper 80/2)
Professor J. Wilesmith (Paper 80/4)

ITEM 1 - CHAIR'S INTRODUCTION

1. The Chair welcomed members of the public to the fifth open meeting, and provided a reminder of SEAC's remit¹. The Chair received apologies for absence from Professor James Ironside, Dr Jiri Safar and Dr Corinne Lasmezas.
2. The Chair thanked the five outgoing members, Professors Aguzzi, Anderson, Kimbell, Masters and Dr Safar for the invaluable contributions they had made to the work of the committee during their periods of membership.
3. The Chair explained that later in the meeting the committee would hold a 20-minute question and answer session for the attending public and would invite the audience to ask the committee about their work.
4. The Chair welcomed Mr David Carruthers (FSA), Professor John Wilesmith (Defra) and Dr Rowena Jecock (Department of Health) who were presenting to the committee.

ITEM 2 – APPROVAL OF DRAFT MINUTES FROM SEAC MEETING HELD ON 26TH JUNE 2003

5. The minutes of the 24 June meeting were agreed subject to amendments provided prior to the meeting by Dr D Matthews (VLA)
 - change paragraph 14 line 3 from “...Dr Matthews informed members that the tongue from the animal that had developed BSE had not been examined...” to read “...Dr Matthews informed members that the tongue from the donor animals had not been examined...”,
 - change paragraph 14 line 4 from “However, tissue from this animal was available for further...” to read “However, tissues from these animals were available for further...”, and
 - change paragraph 26 line 1 from “...source of infectivity, however, peripheral autonomic nerves had...” to read “...source of infectivity, however, cranial nerves had...”.
6. The Chair reminded members that at the previous meeting, the committee had asked the FSA to provide further information on the food use of tongue. Members were informed by the FSA that 99% of tongue is sold as a discrete product, with the remaining 1% incorporated into garnishes and sauces.

¹ The remit of SEAC is 'to provide scientifically based advice to the Department for Environment, Food and Rural Affairs, the Department of Health, devolved administrations, and the Food Standards Agency on matters relating to spongiform encephalopathies, taking account of the remits of other bodies with related responsibilities'.

7. The Chair invited Professor Aguzzi to comment on recent levels and changes in the incidence of sporadic CJD in Switzerland. Professor Aguzzi confirmed that experts from the Swiss Federal Office of Public Health would attend the next SEAC meeting to present data on the surveillance of sporadic CJD in Switzerland. However, the strain typing of the sCJD cases was unlikely to be completed until 2005.

ITEM 3 - REVIEW OF THE USE OF CATTLE BONE IN FOOD PRODUCTION

8. The Chair welcomed Mr David Carruthers from the Food Standards Agency (FSA) to present this item.
9. The committee was asked to provide advice on the infectivity of bone marrow in cattle infected with BSE. By way of background to this request, Mr Carruthers outlined the Beef Bones Regulations, which prevented the sale of bone-in beef to the consumer, and which came in to force in 1997 as a consumer protection measure. The regulations were amended in 1999 allowing the sale of bone-in beef and beef bones directly to the consumer. However, the current regulations specifically do not permit the use of beef bones in processed products, unless the product is sold directly to the consumer from the premises on which it was made. This precautionary approach was taken to protect consumers who might not be aware that they were purchasing products containing cattle bone and would therefore not be able to make an informed choice.
10. Retention of the manufacturing ban had been precautionary but considered prudent due to the possibility that bovine bone marrow might be infective. Consumers wishing to avoid any risk associated with beef bone were protected in circumstances where they might be unable to make a fully informed choice.
11. The data on infectivity in bone marrow was last reviewed by SEAC in November 1998 when the committee considered results from a mouse bioassay examining the infectivity of sternal bone marrow from cattle exposed orally to BSE. BSE infectivity was detected at 38 months post inoculation but was not detected at any other time points in this assay. When the committee considered this issue, they agreed the possibility could not be excluded that the single positive finding could have resulted from experimental artefact, possibly as a result of cross contamination during sampling. It was also possible that an individual animal included in the inoculated pool of tissue carried infectivity that was at a detectable level at a single time point. The committee agreed the positive result could not be discounted, although the risk (if any) from bone marrow was likely to be very small.

12. Following SEAC advice, further investigation on the infectivity of bovine bone marrow has been carried out in the more sensitive cattle bioassay, estimated to be around 500-fold more sensitive than bioassay in mice. Bone marrow samples taken at 32 and 36 months (plus those taken at 22 and 26 months) post exposure to BSE were inoculated intracerebrally into groups of five 4-month old cattle. To date the cattle are still alive at 55-56 months post inoculation with no clinical signs of disease.
13. The single positive result from the original mouse bioassay suggested the level of infectivity was low. Members agreed that the more sensitive cattle bioassay remains the gold standard test for detecting BSE infectivity. Given that bone marrow remains negative in the cattle bioassay at 55-56 months post-inoculation, this suggests that it is unlikely that bone marrow contains significant levels of infectivity. However members noted research published in 1997 reported the expression of PrP in cells of the lymphoreticular system, which suggested that it was theoretically possible that abnormal prion could replicate in lymphoid tissues. Experimental studies by the Institute of Animal Health indicated that haematopoietic cells could carry infectivity, although the level was likely to be low and near the threshold of detection. Given this, members agreed that the single positive report in the mouse bioassay could not be discounted at this point in time.
14. In response to queries about the food use of beef bones and about EU legislation on regulation of beef bones, Mr Carruthers informed members that the most likely use of beef bones in processed foods was in stocks and gravies, although the FSA confirmed it would need to source further information in order to carry out a risk assessment. In terms of EU legislation, there were no EU controls on the use of beef bones in food, with the exception of the skull and vertebral column. As such, the UK legislation was currently out of line with the EU.
15. A member voiced concern about the possibility that removing the ban on the use of beef bones in processed food products may increase the risk associated with other bones (vertebral column) due to residual dorsal root ganglia (DRG) and spinal cord, which might then enter the food chain. Mr Carruthers explained this was the current basis for distinction between the two types of tissue - DRG and spinal cord are known to be highly infective, whereas there is uncertainty about the risk of infectivity in bone marrow. Members asked how this legislation might be enforced to ensure that other types of beef bones did not go into food products, as consumers might not be aware what they were buying. The Chair reminded members it was not within the committee's remit to consider enforcement issues; this was a risk management issue and would have to be considered by the FSA.

16. When the committee was asked if it could quantify the level of infectivity of bone marrow, the Members agreed a more detailed risk assessment would have to be carried out before a more accurate quantification and analysis of bone marrow infectivity could be made. However, they concluded that the risk estimate had been reduced by the results from the more sensitive cattle bioassay. The committee also recommended that it would be prudent to review the bioassay data in mice by using more sensitive methods to look at their brains. Action: FSA

ITEM 4 - REPORT BACK FROM EXPERT PANEL MEETING ON 17TH SEPTEMBER TO DISCUSS UNCONFIRMED RESULTS IN THE UK SCRAPIE SURVEILLANCE SURVEY

17. Professor Bostock, Chair of the Expert Panel, presented this item.
18. A survey published by Defra on the national surveillance of scrapie in Great Britain showed that out of 29,201 animals screened, the TSE status of 28 animals could not be determined due to inconclusive analytical results (28 out of 29,201 abattoir sheep). These animals tested positive by the Bio-Rad Platelia ELISA assay but negative by confirmatory immunohistochemistry (an OIE approved TSE test). At the request of FSA & Defra, an Expert Panel ('the panel'), chaired by Professor Bostock, met on the 17th September 2003 to review these findings.
19. Professor Bostock summarised the panel's conclusions outlined in the formal statement published on the SEAC web site. Members noted that the restrictions of commercial confidentiality meant the panel did not have access to critical data required to assess the preliminary research. Members commented that non-optimal conditions for Proteinase K digestion could lead to false positives in the Bio-Rad Platelia assay. Professor Bostock acknowledged that the panel had considered this possibility but again the lack of details on the experimental reagents meant the panel was unable to assess this.
20. Members were informed that 7 out of the 28 unclassifiable samples in the UK study originated from ARR/ARR sheep, which are considered fully resistant to scrapie. SEAC agreed with the panel's comment that it was not possible at this stage to comment on the significance of these preliminary results for the NSP but endorsed the expert panel's recommendation that infectivity studies in mice using the unclassifiable samples was of high priority. Given the reports of unusual results reported from the UK, Norway (the Nor98 cases) and Germany (two positive results in ARR homozygous sheep) it was suggested that perhaps the case definition of scrapie might be too narrow. Members agreed it was important to determine if these unclassified results represented PrP^c with an intermediate form of a Proteinase K resistance protein, which results from changes in conformation or aggregation state.

21. Professor Bostock informed SEAC that the panel had reviewed the available data on Western blot and immunohistochemistry (IHC) PrP patterns in samples from experimental BSE in sheep. These data did not resemble patterns detected in the UK unclassified samples. The committee noted the panel's further research recommendations to sequence the PrP gene in the unclassified samples to investigate if there was any genetic component to these anomalous results.
22. Members were informed that anomalous results were being detected in different laboratories across Europe using a variety of diagnostic tests. For example, the positive ARR case reported in Germany had tested negative by the Prionics LIA test and positive on the SAF immunoblot and Bio-Rad tests. Members were informed that the French and German investigators have now exchanged reagents, which will allow comparison of the different experimental methodologies. It is not known if the concentration of Proteinase K resistant PrP varies between different tissue sites in the brain. Another complicating factor in terms of interpreting the significance of these results is that different countries adopt different approaches to the selection of tissue target sites for examination using the different tests (screening and confirmatory). To try and control for this in the UK, the sampling method in the UK has been changed recently to allow testing by screening and confirmatory tests on the left and right sides of the obex, which will provide equivalent target sites for different tests. Differences in results will therefore reflect differences in test sensitivity rather than differences in concentration of PrP^{res}. Although there is some agreement amongst EU National Reference laboratories that such an approach should be adopted by all, this is not yet in place.
23. SEAC agreed with the panel's recommendation that animal heads are retained for 24 hours pending the rapid test result to provide additional material for research purposes. However SEAC acknowledged the major logistical issues that this proposal entailed. Members endorsed the panel's recommendation that epidemiological investigations should continue and if any of the unclassified samples originated from farms with previous cases of BSE or scrapie they should be investigated further.

ITEM 5 - EPIDEMIOLOGICAL UPDATE ON BORN AFTER THE REINFORCED BAN (BARB) CASES OF BSE AND DISCUSSION ON THE ORIGIN OF BARBS

24. Professor Wilesmith presented an epidemiological investigation of the 59 cases of BSE in cattle born after 31 July 1996 confirmed in Great Britain up to 6th October 2002, known as born after the reinforced ban (BARB) cases. Professor Wilesmith informed the committee that it was intended to carry out an in-depth analysis of BARB cases approximately every 6 months.

25. The BSE cases originate from 4 surveillance streams: clinical suspects, casualty emergency slaughter animals, fallen stock and cattle slaughtered in the OTMS. The study was restricted to those born in Great Britain (GB) and did not include the 9 Northern Ireland cases born up to 6th October 03, as these cases may have different risk factors to GB cases.
26. The majority of BARB cases (46/59) originated from dairy herds with the remainder reported from beef suckler herds. This proportion was similar to cases in the whole BSE epidemic. In 2002, 58% of BARBS were detected by active surveillance compared to almost 70% up until October 2003. It was noted with concern that some of the animals slaughtered as fallen stock had shown clinical signs of BSE, suggesting that the ability to recognise clinical signs of the disease was declining.
27. The rate of BARBs in the 1996-1997 birth cohort was 97 infected cattle per million (95% confidence interval 54-118) and the 1997-1998 cohort contained 109 infected cattle per million (95% confidence interval 64-170). A large reduction in terms of risk of infection is evident between the 1994-1995 and the 1995-1996 birth cohorts. This is likely to be attributable to the reinforcement of the specified risk material (SRM) controls in MBM. The risk of infection is much lower in the post 1996 cohorts than the pre-1996 cohorts. There is no change in the age of detection of BSE in BARB cases compared to earlier cases.
28. Up until 6th October 2003, 57 BARB cases have been detected, 55 of the cases were detected as singletons and two cases of 2 BARB pairs of animals have been detected in the same herds. Both case pairs were from dairy herds with a previous history of BSE. In the first case pair, the animals were born a year apart. Although it was unlikely both animals received the same batch of feed, it was theoretically possible that cross-contamination of feed occurred. The second case pair was born within a day of each other and it was highly likely both animals were kept in the same pen for the first few weeks after calving and received the same feedstuff.
29. 18 BARB cases originated or were purchased from unrelated herds and 41 animals remained in their natal herds. The analysis showed that 19% of the herds affected had no evidence of previous BSE cases. As herds with a previous high incidence of BSE are not disproportionately represented among the BARB-affected herds, Professor Wilesmith suggested this does not support horizontal or environmental transmission as the predominant route of transmission.
30. The geographical distribution of BARB cases is more uniform compared with the original epidemic and BAB cases. However, the highest incidence of BARB cases was in the South East of England with a statistically significant 3-fold increase in risk compared to other areas, with a lower incidence of BARB cases reported in Northern England.

31. Of the data available on dam survival (50/59 cases), thirty nine (78%) of the dams survived for more than 12 months after the birth of the BARB case. Of the 11 dams that survived less than 12 months after the birth of a BARB case, 6 were part of a normal cull, one was slaughtered in a cohort cull (as BSE had been detected in the cohort), 3 dams were casualty slaughters and one was fallen stock. Thirty six of the 50 dams survived to 5 years of age, which is taken as the mean age of onset of BSE. To date, none of the dams have had other offspring that have developed clinical signs or been detected by active surveillance for BSE.
32. In summarising his conclusions of the analysis, Professor Wilesmith proposed that the incidence of BARB cases was too high to support the hypothesis of sporadic occurrence of the disease. Countries with much larger numbers of cattle have not reported BARB cases. Also the distribution of cases between dairy and suckler herds and the occurrence of two pairs of cases argues against a sporadic cause.
33. Professor Wilesmith suggested that a maternally associated risk factor could not explain the occurrence of the majority of the BARB cases and the dramatic change in geographical distribution for BSE cases born before and after 1996 did not support the environmental argument. The data did not suggest an obvious indication that other risk factors such as abattoir waste and sewage sludge are involved.
34. Professor Wilesmith suggested that the marked change in geographical distribution indicated that the risk of infection was not consistent with previous suspect feed sources. In favour of an exogenous feed source, Professor Wilesmith cited the difference in incidence in beef and dairy herds, the change in geographical distribution for the BARBs compared to cases born before 1996, the absence of MMBM controls in other EU countries until January 2001, the importation of cattle feedstuffs trans-shipped through EU ports, and the greater risk of BARB cases in SE England.
35. In view of the difference in incidence between dairy and beef suckler herds, members asked if any data were available on the nature and origin of the colostrum fed to calves. Colostrum may be pooled or even shared between farms and might possibly represent a source of infection if derived from animals with BSE. Professor Wilesmith noted that the history of colostrum feeding on the "BARB farms" had not been considered but could be included as part of a case-control study.
36. The committee asked how the endogenous feed hypothesis could be investigated. Professor Wilesmith suggested that it might be useful to trace and categorise feed mills that had supplied food to BARB cases and compare this to control herds. Work was in progress on a pilot for the case-control study to investigate mechanisms to trace the source of feed ingredients. However the distribution network could be complex if the ingredients had been trans-shipped through a European port.

37. Members agreed it was very important to look at cases occurring across the EU and in Northern Ireland to pursue any common ground with GB cases and, for instance, other countries with BARB cases such as those reported in Switzerland, where there was robust epidemiological information.
38. The committee endorsed previous recommendations that it was important to sequence the PrP gene of the BARB cases. A Defra spokesperson informed the committee that a research proposal was currently under consideration. A spokesperson for DARDNI confirmed that they intended to genotype the 9 BARB cases detected in Northern Ireland. The committee noted that the availability of material might limit investigation. Only a limited amount of brain tissue was available from a proportion of the GB BARB cases, which may be compromised by autolysis.
39. Members discussed the possibilities of transmission of BSE by environmental contamination in the context of the increased incidence of BARB cases in SE England and commented that it would be useful to sample additional cattle from the BARB herds for further investigation. Professor Wilesmith confirmed that these herds were under constant surveillance.
40. The committee agreed it would prove extremely challenging to design a study that could examine and distinguish the various hypotheses for the source of infection of BSE in BARB cattle. Experimentally, it will prove difficult to distinguish between a low-level feed-borne source and sporadic mutation or low-level environmental contamination. Dr Matthews pointed out that since infection can occur in cattle with as little as a 10 mg dose it would be difficult to trace feed or other exposures at such low levels.
41. In concluding the discussion, the committee agreed that the feed hypothesis is a plausible hypothesis for the origin of the BARB cases, however they could not exclude any of the other hypotheses as being responsible for at least a proportion of the cases. The committee agreed that maternal transmission was a possible explanation for some of the cases, but not all of them, and horizontal or environmental transmission could not be ruled out. The committee recommended that genotyping, biochemical and strain typing studies should be pursued and the epidemiological case-control study on BARB cases should address the issue of colostrum feeding raised by the committee. The committee suggested that it might be helpful to involve members of the SEAC Epidemiology sub-group in commenting on the design of the case-control study.
42. The committee recommended the incorporation of the Northern Ireland BARB cases into the general investigation of BARBs. It was also suggested that collaboration with the Swiss authorities on BARBs would be beneficial.

ITEM 6 - vCJD UPDATE

43. Members were updated on the epidemiology of vCJD in the UK and worldwide. The total number of definite and probable vCJD cases in the UK, as at November 2003, was 143, of which six cases are still alive. No significant sex difference has been observed in vCJD cases with 80 and 63 male and female cases respectively. The mean age at death was 29 years (range 14-74) and the mean age at onset was 28 years (range 12-74). The median duration of illness was 14 months (range 6-40). All cases tested (n=122) are homozygous for Methionine at codon 129 in the PrP gene.
44. No cases of vCJD cases had been reported from non-EC countries for a number of months. To date, six vCJD cases have been reported in France, and a single case in each of Ireland, Italy, Canada and the USA. The vCJD cases reported in France and Italy had not had a history of residence in the UK. The cases reported in Ireland, Canada and the USA had a history of UK residence during the late 80's.
45. The number of onsets and deaths per annum peaked in 1999 and 2000 respectively. The rates of onsets and deaths have showed a declining trend since that time. Statistically, the incidence of vCJD shows a significant departure from an exponential trend to a trend that better fits a quadratic model, which suggests a slowing of the incidence increase and a possible peak in the onset of cases. The quadratic model estimates the current incidence to be 3.2 onsets and 4.1 deaths per quarter and predicts 14 deaths in the next 12 months. The higher level of deaths compared with onsets is expected for an epidemic in decline. The committee agreed the trend of the surveillance data was encouraging but that it remains premature to conclude there is definitive evidence that the epidemic has peaked and that the possibility of future peaks cannot be discounted.
46. The duration of illness for sporadic CJD (sCJD) continues between 1-4 months and between 10-19 months for vCJD. The number of deaths from sCJD per annum has increased from approximately ten per year at the beginning of the 1970s, to about fifty per year in the 1990's. This may be attributed to improved case ascertainment and a similar increase has been observed in other European countries.
47. Members were informed that the committee would be updated on the sCJD surveillance in Switzerland by experts from the Swiss Federal Office of Public Health and National Reference Center for Prion Diseases, at the next meeting in February.

ITEM 7 – ANY OTHER BUSINESS

48. The Chair drew members' attention to two papers provided for information, one of which had recently been published by Professor Aguzzi's laboratory¹.
49. The Chair invited Professor Aguzzi to comment on the implications of his study for iatrogenic transmission of sporadic CJD (sCJD). Professor Aguzzi explained that the study reported the detection of the disease-associated form of prion protein (PrP^{Sc}) in the spleen and muscle of sCJD cases. A more sensitive technique compared to the standard western blot assay was used and as a result the level of prion protein found in muscle in sCJD was about 3 orders of magnitude lower than in brain. It was not known whether the detection of extra-neural pathological prion protein in sCJD was restricted to certain members of the population in Switzerland. It was proposed to carry out the same study to look at the distribution of abnormal prion protein in vCJD.
50. The committee considered a paper² from Professor Collinge's group, which described how the depletion of endogenous neuronal PrP^C in mice with prion infection could reverse early spongiform change, prevent neuronal loss and progression to clinical disease. Members agreed this was an important paper because it demonstrated that mice with significant neuropathological changes showed at least partial recovery from the disease following the depletion of neuronal PrP^C. Members commented that it has been previously thought that prion disease was irreversible once clinical signs had appeared and this progression meant the end of any chance of therapy. Members agreed that the results suggested a more optimistic outlook for the treatment of spongiform encephalopathies.

ITEM 8 – PUBLIC QUESTION AND ANSWER SESSION

51. Mr Jim Clapp had submitted a question for SEAC via the SEAC web site asking the committee to consider his hypothesis that BSE originates from the disposal of human waste on cattle pasture. As Mr Clapp was not present at this meeting the Chair agreed that the secretariat would reply to Mr Clapp in writing.
52. A member of the public asked the committee to comment on the media report of the death of a second vegetarian from vCJD. The Chair commented that the NCJDSU collected dietary histories on vCJD cases. He noted that it was possible that some vegetarians may have been unknowingly exposed to the BSE agent.

¹ Glatzel M, Ott PM, Linder T, Gebbers JO, Gmur A, Wust W, Huber G, Moch H, Podvinec M, Stamm B, Aguzzi A. Human prion diseases: epidemiology and integrated risk assessment. *Lancet Neurol.* 2003 Dec;2(12):757-63.

² Mallucci G, Dickinson A, Linehan J, Klohn PC, Brandner S, Collinge J. Depleting neuronal PrP in prion infection prevents disease and reverses spongiosis. *Science.* 2003 Oct31;302(5646):871-4.

53. A member of the public asked if the committee would recommend caterers, including school and hospital caterers, to choose beef, if the Over Thirty Month Rule (OTMR) were lifted. The Chair replied that SEAC's remit was to provide independent scientific advice to Government on the assessment of risk of TSEs. Following SEAC's advice, Government then evaluate how the advice is best dealt with in terms of management of that risk. As an independent advisory committee it was not appropriate that SEAC should be involved in the subsequent risk management process or that they comment on the implementation of Government policy. The review of the OTMR was the responsibility of the Food Standards Agency (FSA).
54. The FSA informed the member of the public that the decision on changing the OTMR was made following the public consultation exercises and the public meeting of the FSA board in July 2003. In the event that the OTMR were lifted, the main plank of the public health protection measure, i.e. removal of specific risk material (SRM) would remain in place. The BSE testing programme would also add an additional level of consumer protection.
55. A member of the public asked the committee about the effectiveness of the BSE screening tests. The committee explained that cattle may become infected early in life but the test is only sensitive when animals are relatively late in the incubation period, which means the tests cannot be considered 100% sensitive. However, the OTMR review had considered the most pessimistic of scenarios of infectivity entering the food chain in the event of the tests failing to detect infected animals. The committee agreed that more research was required to improve the sensitivity of diagnostic tests so that infected animals could be detected earlier during the incubation period.
56. The FSA stated that the specified risk materials (SRM) were removed from all the cattle slaughtered for human consumption. Removal of SRM removes about 99% of the infectivity from animals. Therefore, the BSE testing programme is implemented as a further measure to protect public health.