



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Minutes of the 82nd meeting held on 29th April 2004

At

The Conference Centre
Holiday Inn Bloomsbury
Coram Street
London
WC1N 1HT

Members: Professor P. Smith (Chair)
Mr. J. Bassett
Professor C. Bostock
Dr. D. Brown
Mr. C. Browne
Professor R. Carrell
Dr. J. Chambers
Professor N. Hooper
Professor J. Ironside
Mr P. Jinman
Dr. C. Lasmezas
Dr. J. Manson
Professor I. McConnell
Ms. D. McCrea
Dr. G. Medley
Dr. P. Rudge
Professor M. Stanley

Assessors: Dr. J. A. Bailey (DEFRA)
Mr A. Harvey (FSA)
Dr R. Jecock (DH)

Technical Advisors: Dr P. Barrowman (Defra)
Ms. A. Conroy (FSA)
Dr S. Dixon (FSA)
Mr P. Soul (Defra)

Dr J. Stephenson (DH)
Dr D. Matthews (VLA)

SEAC Secretary: Dr C. Boyle

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

Also in attendance: Mr P Comer (Paper 82/3)

ITEM 1-CHAIRS INTRODUCTION

1. The Chair welcomed members of the public to the seventh open SEAC meeting, and provided a reminder of SEAC's remit.¹ The Chair noted apologies for absence from Professor Graham Bulfield.
2. The Chair welcomed two new members, Ms Diane McCrea, an independent consultant on food and consumer affairs, who was unable to attend the last meeting, and Professor Margaret Stanley, Professor in epithelial biology at the University of Cambridge, who had been appointed to SEAC since the last meeting.
3. The Chair welcomed Dr Mandy Bailey (Defra), and Mr Phillip Comer (DNV Consulting), who were presenting items to the committee. The members were reminded of their obligation to declare conflicts of interests at the start of each agenda item.
4. The Chair informed the committee that the meeting was being filmed as part of a one-year trial of web casting SEAC open meetings to assess the potential benefits and likely uptake of viewing the meeting via this medium. This initiative continued SEAC's commitment to expanding openness.

ITEM 2- APPROVAL OF DRAFT MINUTES FROM SEAC MEETING HELD ON 25TH FEBRUARY 2004 SEAC MEETING (SEAC 81) AND MATTERS ARISING

5. The minutes of the 25th February meeting were agreed as a correct record subject to the following amendments:
 - change paragraph 34 line 18 from "*bovine amylotic spongiform encephalopathy..*" to read "*bovine amyloidotic spongiform encephalopathy..*",
 - change paragraph 40 line 6 from "*there were around 200 historical samples..*" to read "*there were several hundred historical samples..*",

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'.

- change paragraph 42 line 3 from “...sensitive WB technique.” to read “...sensitive WB technique and IHC.”,
- change paragraph 42 line 4 from “...other than on clinical cases.” to read “...other than on clinical cases, as they were the only animals from which whole brains were available.”

In considering matters arising from the minutes the following issues were noted:

6. At the 25th February meeting the committee was informed that an *ad hoc* epidemiological sub-group meeting was scheduled for the end of March 2004 to discuss the design of a case-control study investigating the Great Britain and Northern Ireland BARB cases. The Chair reported that good progress was made at this meeting and that the minutes would be circulated to SEAC in due course.
7. At the 25th February meeting, SEAC discussed the possible case of vCJD transmitted by blood transfusion (Item 3) and the potential measures being considered by the DH. Members were informed that the Department of Health and the National Blood Service now no longer collect blood donations from donors who had previously received blood transfusions in order to minimise the risk of transmission of vCJD by blood transfusion.

ITEM 3-USSES OF UK COLLAGEN FROM HIDES OF UK CATTLE

8. Dr Mandy Bailey (Defra) introduced the item by explaining that current UK domestic legislation (The Bovines and Bovine Products (Trade) Regulations 1999) prohibits the use of collagen sourced from the hides of UK bovines for non-technical uses. This requirement was introduced as a risk management measure to ensure compliance with the UK export ban on beef and beef products. It goes beyond current EU legislation, which allows collagen to be used for a wide range of products falling under the definition of non-technical uses. A UK based company producing collagen has submitted a request to Defra to re-commence sourcing of collagen from the hides of UK bovines. This would require an amendment to domestic legislation. The committee was asked to consider the risk implications if the UK legislation was amended to allow the sourcing of collagen from the hides of UK bovines for non-technical use.

9. Members were informed that collagen is currently sourced from the hides of bovines from other EU countries; therefore it was important to consider the relative risks of collagen sourced from the hides of UK bovines compared to collagen sourced from bovine hides in other EU countries. The hides to be used for collagen production would come only from animals fit for human consumption, which in the UK currently means only animals under 30 months of age. Should the Over Thirty Month (OTM) rule change, however, then animals over the age of thirty months would be tested and a negative result required before the hide could be used.
10. One member sought clarification on the end use of collagen and whether it would also be used in bovine feed or bovine veterinary products. Dr Bailey explained that the legislation requiring change related to trade issues and that other legislation would still be in place to govern the end use of collagen, such as in animal feed. Mr Peter Soul (Defra) confirmed that there was no possibility of using collagen as a livestock feed ingredient, although it could be used, under special circumstances, for encapsulating certain veterinary medicines. Dr Rowena Jecock (DH) clarified that separate EU legislation existed for collagen used in pharmaceutical and medical devices. Similar to animal feed, pharmaceuticals and medical devices fall under the definition of non-technical uses, but this does not mean that collagen sourced from the hides of UK bovines would be used in such products. The only pharmaceutical product reported to DH to contain collagen was an anti-dandruff shampoo.
11. Dr Bailey explained that in considering the relative risk of collagen sourced from the hides of UK bovines, it was important to recognise that the number of BSE cases born after 1996 in the UK was comparable to that of other EU countries. One member asked for information on the EU countries that supply the UK based company with raw material for collagen production. Mr Stan Sadowski (Defra) confirmed that Spain and Eire were two examples of EU countries supplying the UK based company with bovine hides and skin for the production of collagen. Both countries have a comparable post-1996 BSE prevalence to that of the UK. With the exception of Portugal, which like the UK has a beef products export ban, the company could source raw material for collagen production from any EU country. Other legislation existed in relation to sourcing collagen from non-EU countries.
12. Members sought clarification on the sourcing of hides from other EU countries and whether only hides from animals that are tested as BSE negative were used. Members were informed that given the OTM rule, only animals under the age of thirty months are allowed

into the food supply in the UK. As such, only the hides of those animals at present would be used for sourcing collagen. The position in other EU countries is different since they do not have an OTM rule and are therefore required to test those animals over the age of thirty months going into the food supply. Should the OTM rule change; the UK would also be required to have a testing regime in place. Members agreed that on a relative risk basis, collagen sourced from the hides of UK bovines would present a similar risk to those EU countries with a comparable BSE prevalence providing other factors such as processing and sourcing were also similar.

13. Members expressed concern about the possibility of changing legislation whilst the UK continued to be classified as high risk with respect to BSE. One member commented that the SSC opinions emphasised the need for safe sourcing. Allowing UK hides to be used in the manufacture of collagen would be allowing sourcing from high-risk areas. Dr Danny Matthews (VLA) commented that the classification was a historical relic. With improved knowledge, there is now a greater willingness to amend international trade rules in recognition that certain commodities can be traded safely irrespective of the source country. Dr Matthews explained that it was important to consider the risk of the actual product or by-product rather than consider risk classification alone.
14. In response to one member's request for further information on the risks associated with bovine hides and skins, the Chair informed members that the research to date had not detected infectivity in bovine hides. Latest data from the VLA pathogenesis study showed no evidence of transmission from bovine skin incubating BSE at 18, 26 and 32 months post infection. As such, bovine skin was currently classified by the World Health Organisation (WHO), as a tissue with no evidence of BSE infectivity. One member commented that the most likely route of infectivity would be due to contamination with brain tissue at slaughter. Mr Soul explained that the whole head including the head hide is classified as SRM in the UK. As the head hide was most likely to be contaminated, removal of the head meant that the risk of cross contamination in the UK was less than in other EU countries where the head hide may be used.
15. Members commented that a small number of animals may enter the food chain carrying infectivity and that in terms of cross contamination, the most likely route would be via brain material leaking from the stunning wound of such animals onto the hide. The identification of hides was imperative and should an animal test positive, it would be important to ensure that the hide from the positive animal could be identified and destroyed. The Chair

explained that, in other EU countries, hides are kept in batches and the whole batch destroyed if a positive sample result is returned for one of the animals in the batch. Members were informed that the UK would introduce a system to ensure hide identification should testing replace the OTM rule. Members were also informed that hides originating from animals considered fit for human consumption, would also undergo an acid and alkali treatment reducing any potential infectivity by approximately 4 logs.

16. In order to consider the effect of inactivation on infectivity, members requested further information about the processing techniques used in the production of collagen. Members asked whether the processing techniques used by the UK company were similar to those in other EU countries. The Chair commented that the SSC had been reluctant to come to a conclusion on infectivity inactivation given the variety of processes that exist. Dr Irene Hill (FSA) confirmed that where collagen is traded between EU countries, the processing requirements, such as the amounts of acid and alkali to be used, are specified.
17. One member asked for further information relating to the reference of a paper in print by Cunningham *et al*, which reports the finding of infectivity in the skin of the greater kudu. The member also asked about the sourcing of collagen for ophthalmic use and implantable devices and whether the source must be from Geographical BSE Region (GBR) 1 countries. Dr Danny Matthews provided further information on the kudu findings. The kudu had died in the early 1990s and tissues were inoculated into mice to assay transmissibility. He explained that the kudu has a TSE pathogenesis more like ovines than bovines with a far wider involvement of the lymphoreticular tissues. On the issue of collagen for ophthalmic use or medical devices, Dr Rowena Jecock confirmed that over-arching legislation existed for pharmaceuticals and medical devices, which requires manufacturers to go through rigorous risk management controls. Each product is assessed on a case-by-case basis.
18. In conclusion, the Committee agreed that in respect of the proposed use of collagen sourced from the hides of UK bovines for use in food, the potential risk would be minimal given that collagen would be sourced from those animals considered fit for human consumption. In considering the risk implications for use of collagen sourced from the hides of UK bovines in pharmaceutical and medical products, however, the committee requested additional information on the legislation governing end-use. The committee also requested further information on i) the collagen production

process in order to assess infectivity inactivation, and ii) the prevalence of BSE in the UK and other European countries so that they could consider the relative risk of sourcing European versus UK derived bovine material. In considering relative risk, it would be important to consider the UK position both pre and post changes to the OTM rule.

ITEM 4-SURVEY OF HISTORIC BUTCHERY PRACTICES

19. The Chair welcomed Philip Comer of DNV Consulting to present the findings of the report to the committee.
20. The Chair informed the committee that the survey had been conducted following an investigation by Leicestershire Health Authority (LHA) into the variant CJD (vCJD) cluster in Queniborough. The report of the LHA concluded that there was an association between the vCJD cases and consumption of beef purchased from butchers where there was a risk of cross-contamination of beef carcass meat with bovine brain.
21. Following SEAC advice, the Food Standards Agency (FSA) had commissioned DNV Consulting to carry out a GB wide survey of those butchery practices identified in the LHA report.
22. Mr Comer explained to the committee that the main aim of the survey was to determine the UK prevalence of butchery practices as identified in the LHA report and in addition to determine to what extent practices may have changed over time. The survey would also assess the impact of any legislative changes during the specified time period under investigation (1980-1995) and consider any other factors related to butchery practices that may have affected exposure to infectivity.
23. Information was collected from face to face interviews with butchers and abattoir workers [n=84] from six areas representative of different regions (Northumberland, Central Scotland, North West England, South Yorkshire, the Midlands and the South West) of GB but which focussed on rural areas. Other professions within the meat trade were also interviewed during the survey, which included environmental health officers, meat inspectors, vets and farmers. The investigators were concerned that butchery practices as identified by LHA were more likely to be practiced by small butchers and thus would tend to be under-reported because of the time elapsed and the likelihood that these premises no longer existed.

24. In all areas, between 15 – 40% of butchers slaughtered cattle for their own shops. The only major difference in the types of premises examined was in Scotland, where small abattoirs did not exist and cattle were slaughtered at larger, more centralised abattoirs.
25. Local butchers investigated during the course of the survey had been routinely harvesting the brains of locally reared, slaughtered cows of average age of 24 months but some up to 36 months. The use of knives in abattoirs was examined as a source of cross contamination. The head was often removed very quickly following slaughter and was usually done in a separate area to the cutting of the carcass. In larger abattoirs, slaughter men would have their own set of knives and it was unlikely that they would have been shared. In small abattoirs sterilisation of the knives tended to be basic, often consisting of a water rinse.
26. The survey found that butchers in the South West of England and the Midlands were routinely harvesting the head and brains of cattle. The brains were harvested for direct sale to consumers. The only use of brain in a meat product was found in Northumberland where butchers used them in potted meat. No other practices were found that were considered to have been high risk. These butchers tended to use prime stock so the BSE risk would have been low. No statistical analysis had been carried out to see if there were any differences in the numbers of vCJD cases in areas where brains were harvested, as the numbers of cases were too small to be meaningful.
27. Head meat was considered a valuable product and was used in some minced meat products, but some would have also been used for pet food. The smaller butchers processed the heads themselves, usually at the end of the day, so there was less potential for cross-contamination. The larger abattoirs would have sent them on to specialised head boners. It was found that these would have been sent in the same van as heads from cull stock (older animals), so there was potential for cross-contamination. Not all head boners removed brains, but when they did the brains were mainly exported outside the UK.
28. Members noted the export of brains to France, but observed that there did not appear to be a corresponding increase in vCJD cases in the country. Members were informed that as the French consumer prefers meat from older cows, an increase in the number of vCJD cases would have been expected given the increased likelihood of exposure to infected meat.

29. Members asked about the UK distribution of high-risk products identified in the survey. Mr. Comer informed members that the country's main meat market, Smithfield was primarily exporting brains to France, so these would not have been for domestic use. Members asked for clarification on why the authors of the survey had concluded that because many butchers and abattoirs were slaughtering prime stock, the overall BSE risk was low. Mr. Comer informed members that this conclusion was due to the age of the cattle at slaughter, rather than the breed of the animals. Generally, the cattle were under 30 months so the titre of BSE infectivity would have been low.
30. Members asked if the survey had found the butchery practices in Leicestershire were any different to other practices around the UK. Mr. Comer explained that the harvesting of brains and use of the same knives for different purposes were the only common practices in Leicestershire, the South West and the Midlands. Members agreed that basic cleaning of knives was unlikely to eliminate any infectivity present.
31. The study had reported that butchers recalled that most of the brains were sold to older customers. The survey results suggested that it was unlikely that younger age groups consumed brain directly, but may have been exposed if brain was contained in other food products. Mr. Comer explained there had been no evidence that brain was deliberately used to make burgers or sausages.
32. Members asked about whether the removal of head meat by suction under high pressure was a common procedure. It was explained that at one time, unlike brain, the head was not classified as Specified Risk Material (SRM), and abattoirs used this method to remove the brain so they could use the head. This practice is thought to have occurred between 1989-1992 before the legislation was amended. It had been recognised that the method was contaminating carcasses *per se*, rather than just the head.
33. Dr Matthews informed members that the Specified Bovine Offal (SBO) ban in 1989 had revealed that central nervous tissue (CNS) tissue was being used in sausages and some other meat products. This suggested that the people interviewed in the survey might not have been able to accurately recall practices that have since been banned. Mr. Comer agreed but explained that inaccuracies in reports could be attributed to the difficulty in recollecting past butchery practices dating back over twenty years.

34. The Chair reminded members they were being asked if this information presented any new insights into the route of infection of vCJD.
35. Mr. Comer concluded that butchery practices in Queniborough were not extraordinary when compared to the rest of the country. The survey had found that it was likely that brain material from older animals would have been exported outside of the UK. Heads collected for processing by head boners included heads from older animals together with those from younger animals possibly resulting in cross- contamination of the head meat.
36. A member asked about the investigation into the Queniborough cluster of vCJD cases where it was thought one butcher in the area was providing brains to a local restaurant and this might have been a risk factor for disease.
37. The Chair commented that there had been no observed increase in the number of vCJD cases in populations such as UK older consumers.
38. The Chair concluded that the study had provided some useful insights into the butchery practices carried out at the height of the BSE epidemic, but it did not provide any additional information about the route of infection of the BSE agent in humans.

ACTION: Secretariat to provide members with a copy of the LHA report.

ITEM 5- VCJD UPDATE

39. Members were updated on cases of vCJD in the UK and worldwide. The total number of definite and probable vCJD cases in the UK, as at April 2004, was 146, of which 5 cases are still alive. There had been no new cases in 2004. No significant sex difference has been observed in vCJD cases with 82 and 64 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 remained at 14 months (range 6-40). All cases tested (n=124) are homozygous for methionine at codon 129 in the PrP gene.
40. 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 did not have a history of residence in the UK. No new cases of vCJD had been reported in

France for over a year. The cases reported in Ireland, Canada and the USA had a history of UK residence during the late 1980's.

41. The number of onsets and deaths per annum peaked in the UK in 1999 and 2000 respectively. 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 estimate the current incidence of onsets to be 1.6 per quarter and deaths to be 2.7 per quarter with 8 deaths predicted in the next 12 months (95% prediction interval 3 to 15).
42. SEAC was informed that a plateau model could also be applied to the observed quarterly incidence of deaths, estimating 4.8 deaths per quarter and 19 deaths in the next 12 months with a 95% prediction interval of 9 to 29. 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.
43. The duration of illness for sporadic CJD (sCJD) continues between 1-4 months and between 10-19 months for vCJD. The mean age at death was 66 years (range 20-95) and the mean age at onset was 66 years (range 15-94). The median duration of illness is 4 months (range 1-74). Of the sCJD patients genotyped, 66% and 17% are methionine and valine homozygotes respectively and, 17% are methionine/valine heterozygotes. 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.
44. Professor Ironside from the UK National CJD Surveillance Unit agreed to present data on the geographical distribution of vCJD in the UK at the next meeting.

ITEM 6- REVIEW OF BSE STRAIN TYPING

45. The Chair informed members that the secretariat had provided a review of BSE strain typing and accompanying papers (Paper 82/4) for information. Dr Jean Manson had agreed to present a research update on strain typing at the next SEAC meeting. Members were invited by the Chair to contact the secretariat regarding any BSE strain typing issues they wished to include for discussion at the next meeting.

ITEM 7- ANY OTHER BUSINESS

46. Members were provided with two papers published in the journal Nature, by King & Diaz-Avalos¹ and Tanaka *et al*², demonstrating that in yeast a single prion protein can adopt different conformations to form transmissible particles that propagate different yeast prion strains, independently of nucleic acid.

47. Members commented that the published findings provided a proof of principle for the prion hypothesis, which requires that prions can change conformation into a self-propagating form without the need for nucleic acid. However members considered that such evidence in yeast had to be applied with caution to the pathogenesis of mammalian prion diseases. The committee noted that unlike yeast prions, the mammalian prion protein has both a repeating N-terminal region and a glycosylated C-terminal half, and although the N-terminal region may influence the conformation of the C-terminal region³, it is the latter that is critical for transmission of disease.

¹ King CY, Diaz-Avalos R. Protein-only transmission of three yeast prion strains. Nature. 2004 Mar 18;428(6980):319-23.

² Tanaka M, Chien P, Naber N, Cooke R, Weissman JS. Conformational variations in an infectious protein determine prion strain differences. Nature. 2004 Mar 18;428(6980):323-8.

³ Lawson VA, Priola SA, Meade-White K, Lawson M, Chesebro B. Flexible N-terminal region of prion protein influences conformation of protease-resistant prion protein isoforms associated with cross-species scrapie infection in vivo and in vitro. J. Biol Chem 2004 Apr 2; 279(14): 13689-13695