



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Draft open minutes of the 97th meeting held on 10th May 2007

Royal Horticultural Halls and Conference Centre
Greycoat Street
London
SW1P 2QD

Members: Professor C. Higgins (Chair)
Mr. J. Bassett
Professor D. Brown
Dr. A. Ghani
Professor N. Hooper
Mr. P. Jinman (Deputy Chair)
Dr. R. Knight
Professor C. Lasmézas
Professor J. Manson
Ms. D. McCrea
Professor G. Medley
Professor J. Nicoll
Dr. R. Salmon
Professor A. Williams

Assessors: Dr. A. Douglas (DARDNI)
Dr. A. Gleadle (FSA)
Mr. M. Noterman (DH)

Technical Experts: Dr. P. Bennett (DH)
Mr. P. Burke (Defra)
Miss. A. Conroy (FSA)
Dr. S. Dixon (FSA)
Professor N. Gill (HPA)
Dr. I. Hill (FSA)
Dr. D. Matthews (VLA)
Dr. J. Stephenson (DH)

SEAC Secretary: Miss K. Richards

Secretariat: Dr. T. Barlow
Mr. B. Cole
Dr. D. Cutts
Dr. P. Keep
Dr. C. Ravirajan

Also in attendance Dr. S. Hill (Defra)
Dr. S. MacDiarmid (Ministry of Agriculture and
Fisheries, New Zealand)

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ITEM 1 – CHAIR’S INTRODUCTION

1. The Chair welcomed everyone to the 97th meeting of SEAC. He welcomed the new members Drs Azra Ghani, Richard Knight and Roland Salmon onto the committee for their first meeting. Dr Ghani is Head of the Mathematical Epidemiology of Infectious Diseases Group at the London School of Hygiene and Tropical Medicine and member of the SEAC Epidemiology Subgroup, Dr Knight is a consultant neurologist and Director of the National Creutzfeldt-Jakob Disease (CJD) Surveillance Unit, and Dr Salmon is Director of the Communicable Disease Surveillance Centre in Wales. Professor John Collinge, a consultant neurologist and Head of Department of Neurodegenerative Disease at the Institute of Neurology, University College of London and Director of the Medical Research Council – National Prion Unit, has also been appointed to the committee but sent apologies for absence. The Chair also welcomed the experts in attendance to present their research to the committee.
2. The SEAC Secretary explained that open meetings allow the public an opportunity to observe the committee at work and provide an insight into how an advisory committee provides independent scientific advice to Government. Government officials with responsibility for Transmissible Spongiform Encephalopathy (TSE) policy may be invited to contribute to discussions. The committee will hold a reserved business session in the afternoon to allow discussion of unpublished studies on unusual cases of BSE and ongoing research on possible transmission of variant CJD (vCJD) via dentistry. This is in accordance with the SEAC Code of Practice. Short summaries of the open and reserved business discussions would be published on the SEAC website.
3. A list of website addresses for recently published reports relevant to TSEs has been tabled, including web addresses for the Clinical Governance Advisory Group report and the Department of Environment Food and Rural Affairs (Defra) TSE research programme review. Members had been sent two CDs. One provided by the Veterinary Laboratories Agency (VLA) contains video clips of the clinical signs of atypical and classical scrapie. The second is of the Food Standards Agency (FSA) Research and Surveys Annual Report for 2006.
4. The next SEAC meeting is scheduled for Friday 20th July 2007 in London at the Royal Horticultural Halls and Conference Centre.

5. Members were reminded that they are obliged to declare any commercial or other interests they may have at the relevant agenda items and to inform the secretariat of any changes to the register of members' interests. Expense claims should be submitted as soon as possible after meetings and must be submitted within three months of meetings.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 96 (SEAC 97/1)

6. The minutes of SEAC 96 were agreed as a correct record.

ITEM 3 – CURRENT ISSUES

7. SEAC was informed about the following issues, both of which were discussed later in the agenda:

- United Kingdom Chief Dental Officers recently issued guidance to dentists to limit certain dental instruments to single use as a precautionary measure to reduce the potential risk of variant Creutzfeldt-Jakob Disease (CJD) transmission¹.
- The first unusual case of Bovine Spongiform Encephalopathy (BSE) in the UK.

ITEM 4 – ATYPICAL SCRAPIE CASE AUDIT (SEAC 97/2)

8. The Chair explained that, at SEAC 95, members were informed of a case of atypical scrapie in a UK research flock previously considered free of TSEs as the founder animals had been imported from New Zealand, a country considered to be free of TSEs. At SEAC 96, SEAC had been updated on the progress of an audit into procedures used to manage the flock and investigations into the possible origins of the case.
9. Dr Steven Hill (Defra) informed members that Defra's Chief Scientific Adviser had commissioned an independent audit to investigate whether the case had arisen from inadvertent substitution of samples or whether breaches of biosecurity had occurred at the research site. The United Kingdom Accreditation Service (UKAS) had conducted the audit, visiting the site and examining records in November 2006. A draft report was submitted to Defra and VLA on 10th January 2007. Defra and VLA had responded to UKAS on 14th February 2007 and the final

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<http://www.gnn.gov.uk/environment/fullDetail.asp?ReleaseID=279256&NewsAreaID=2&NavigatedFromDepartment=False>

report, amended to take account of responses by VLA and Defra, was published by UKAS on 16th April 2007². UKAS concluded there was no evidence of errors in the collection of samples for testing, or any major breaches in biosecurity during the importation or maintenance of the flock. Minor issues with sample handling and record keeping were identified but it was considered highly improbable that any sample substitution had occurred. There were a number of minor biosecurity issues over the 10 year period since the sheep were imported, including perimeter fencing being too low initially, application of sewage sludge to one area of land (although this land was not accessed by the sheep), possible breaches of biosecurity with respect to contractors coming onto the site, instances of access by crows, foxes and vermin, and a perceived lack of disinfection of lorries between delivery of feedstuff consignments. The incidence of non-TSE diseases on site was examined as an indicator of whether breaches of biosecurity had occurred.

10. Dr Danny Matthews (VLA) informed members of the VLA response to the final audit report. The expertise of UKAS in auditing was acknowledged. However, the scope of the audit did not allow for the determination of the origin of the case. Although scientific investigations by VLA are ongoing, it was acknowledged that it may not be possible to come to firm conclusions about the origin of the case. In relation to the minor breaches of biosecurity, it was inevitable that the flock would be exposed to birds and rodents. However, due to the low population of sheep and the absence of classical or atypical scrapie in the surrounding geographical area, these exposures are unlikely to have resulted in the introduction of atypical scrapie. Further investigations into the ingredients in feedstuffs supplied to the farm are underway to determine whether these could have resulted in transmission. The potential risk from experimental spreading of sewage sludge on the farm was mitigated by three facts: sludge was not spread on fields where sheep had access; it was deliberately applied in a manner that would minimise risk of aerial dispersal; and these fields are lower than the fields in which the sheep were kept so dispersal of the sludge to these areas was unlikely.
11. Dr Matthews explained that a putative second case of atypical scrapie in this flock was being investigated. Initial investigations had suggested this was not a true case but one which may have arisen as a result of cross-contamination of samples in bioassay

² http://www.defra.gov.uk/animalh/bse/othertses/scrapie/nsp/pdf/assessment_report.pdf

experiments. Another laboratory had been asked to perform inoculations with this isolate and this study continues.

12. Dr Matthews gave an overview of the parentage of the confirmed and putative cases of atypical scrapie. The confirmed case was a six year old cheviot sheep of AFRQ/AFRQ genotype. Its biological dam was an imported ARQ/ARQ sheep and its classical scrapie status was unknown prior to importation from New Zealand. The ARQ/ARQ sire was also imported and was clinically normal on importation. The surrogate dam, also imported, was of ARQ/ARR genotype and was also clinically normal on importation. The putative case was a 32 month old homebred ARR/ARR Poll Dorset sheep. Its dam was homebred and classical and atypical scrapie negative at post mortem examination. Its sire was imported from New Zealand and its classical scrapie status at this time was unknown. It has since been exposed after leaving the breeding flock. The 62 month old twin of the putative case was still alive and had been isolated for observation.
13. Dr Matthews gave an overview of the number and genotype, age and breed distributions of sheep that had been imported from New Zealand and animals from the flock that had been included in VLA research projects or supplied to other research institutes. A database had been set up to link the destination of imported and home bred sheep and the fate of their tissue samples. Tissues from 916 sheep had been tested by immunohistochemistry (IHC) with only the confirmed case testing positive. Screening of cerebellum samples from 579 of these sheep by more sensitive enzyme linked immunosorbent assay (ELISA) did not reveal further positive results. Many of the samples were from sheep under four years old and therefore probably too young to detect atypical scrapie. The power of the investigation was limited by the number and age of the animals. UKAS had noted that VLA had decided not to examine all culled sheep. Most were in fact surplus lambs aged under 12 months and therefore were unlikely to test positive for atypical scrapie if infected.
14. Dr Matthews indicated that VLA would review the raw data in light of the UKAS report, and all conditions for the supply of materials to the flock. The database constructed to trace animals from the flock is an asset that would continue to be developed.
15. A member asked for clarification of the tests used on the confirmed and putative cases. Dr Matthews explained that the putative case had been negative by IHC, western blot and ELISA but positive by mouse bioassay at the VLA, although parallel inoculations at two

other institutes were incomplete, they had not yet revealed evidence of infectivity. The confirmed case had not been tested by bioassay but was positive for atypical scrapie by IHC, western blot and ELISA. The member considered it important to confirm whether the putative case was infected with atypical scrapie.

16. A member noted that the flock was a valuable resource and asked about additional biosecurity measures. Dr Matthews indicated that, beyond having a closed flock, it would be extremely difficult and costly to protect sheep from being exposed to all potential infection factors.
17. A member noted that orf (a viral disease of small ruminants) could be used as a model to investigate the spread of diseases like classical and atypical scrapie in the flock. Dr Matthews indicated that non-TSE diseases are not necessarily easy to identify and there were logistical problems with testing sheep prior to arrival.
18. Members asked about the vaccination status of the imported sheep and whether it was possible a vaccine contaminated with atypical or classical scrapie may have been used. Dr Stuart MacDiarmid (MAF New Zealand) indicated that the New Zealand authorities had not investigated the vaccination history of the flocks of origin. If vaccine had been the source of infection of atypical scrapie, it was likely multiple cases would be observed in flocks. Dr Matthews commented that Veterinary Medicines Directorate scrutiny of veterinary medicines imported from New Zealand and Australia was very thorough. He indicated that it would be possible to provide a vaccination history for the sheep.
19. A member noted there was little information regarding sheep shearers that had visited the farm or their equipment and that this was a risk factor in some sheep disease transmission. A member noted that another research study had concluded that shearing was unexpectedly protective against classical scrapie infection.
20. A member noted that there had also been a case of atypical scrapie of unknown origin born in 1989 in a closed sheep flock at the Neuropathogenesis Unit, Roslin Institute.
21. Members agreed that the audit had not found evidence for inadvertent substitution of samples at the site and that the minor breaches of biosecurity were unlikely to have caused the infection. There was no evidence to suggest any particular route by which the case had become infected and the possibility of a spontaneous origin could not be excluded. The effect of the case on research

projects was likely to be minimal as no other cases had been confirmed. There was no evidence that the case had originated from New Zealand.

22. In response to a query submitted by the Chief Veterinary Officer, members agreed there was little additional to be learned regarding maintaining national biosecurity. In addition, conclusions could not be drawn on the origin of the case and the possibility that it was a spontaneous case remained.

ITEM 5 – ATYPICAL SCRAPIE RESEARCH (SEAC 97/3)

23. Dr Irene Hill (FSA) explained that in June 2006 the FSA Board gave consideration to current precautionary risk management measures for small ruminants. The Board agreed that current measures were sufficient but requested that a contingency plan be developed in case understanding of the risk of atypical scrapie to human health changed. SEAC was presented with a paper on possible atypical scrapie research or surveillance results that may produce a change in understanding of the human health risk. SEAC was asked to view the paper, which raised a number of questions, as a horizon scanning exercise to inform the contingency plan. It was recognised that experimental methods and results would need to be reviewed in detail by SEAC when they emerged before any conclusion about the risk could be made.
24. Question one related to changes in the prevalence of atypical scrapie. Members considered that changes in prevalence would be most significant if concomitant changes occurred in the prevalence of new types of CJD cases. However, it was acknowledged that, because of the long incubation periods of prion diseases, such changes may take years or even decades to emerge. Surveillance should continue so that any changes in prevalence of CJD types can be detected.
25. Question two related to the implications of finding atypical scrapie in countries previously thought to be free from classical and atypical scrapie. Members noted that in the absence of any data which suggests a link between types of CJD and atypical scrapie such a scenario would not change the assessment of risk.
26. Question three related to the perception of risk should atypical scrapie be found to have a similar epidemiology to classical scrapie. Members responded that if historic data show the disease had been around for many years this may suggest the risk was low, however the long incubation period of human prion diseases

made it impossible to draw firm conclusions at this time. It was noted that the earliest atypical scrapie case identified was from 1989 highlighting that this is not a very new disease. Members considered it important to continue to assess the prevalence of atypical scrapie and that historic sheep samples be analysed for the presence of atypical scrapie. Dr Matthews noted that atypical scrapie had now been found in the United States of America.

27. Question four asked what significance should be attached to analysis of historic samples if results show similar biochemical profiles to recent cases. Members considered that this was dependent on whether surveillance suggested that atypical scrapie was associated with CJD. Question five asked whether the 1989 case of atypical scrapie in the UK heightens concern that this was a newly emerged disease that had spread and whether humans may be incubating the disease without having developed clinical disease. Members considered that this was possible but, perhaps unlikely.
28. Questions six to 10 considered the interpretation of results from transmission experiments of atypical scrapie, BSE and classical scrapie in mice. Members responded that although transmissions would be suggestive of a risk, especially in experiments using humanised mice, the level of risk would be difficult to determine without comparative studies with other TSEs using the same model. Strong evidence of a risk would only be obtained if similar results from comparative studies were obtained in more than one model were obtained, this would provide strong evidence of a risk. Members also considered it important that transmission studies be conducted in ovinised mice of all sheep prion protein genotypes to assess transmissibility between sheep. If secondary but not primary passage of atypical scrapie lead to transmissions in humanised mice, members agreed it would be important to conduct further subpassages and compare the behaviour of atypical scrapie with other TSEs in these studies.
29. Questions 11 and 12 related to the interpretation of transmission of atypical scrapie in non-human primates. Members noted that non-human primate models are all methionine homozygous at codon 129 of the prion protein gene and therefore, unlike humanised mice, gave data relating only to one genotype. However, unlike mice, the immune and lymphoreticular system of non-human primates were closely related to those of humans. Thus, data from non-human primates and humanised mice would provide complementary data and together provide a better assessment of the risk than data from one type of model. However, the route of

administration was critical and experiments using the oral route are the most relevant to human exposure.

30. Question 13 considered the significance of experiments investigating the conversion efficiency of abnormal prion protein (PrP^{Sc}) in converting normal or recombinant human PrP to the protease resistant form. Members considered that data from these experiments do not always correlate well with the *in vivo* situation, although they do provide an indication of whether conversion is possible, particularly when confirmed by results from mouse transmissions.
31. In relation to question 14, members considered that data from studies to assess the PrP^{Sc} and infectivity distribution in tissues would be very important if atypical scrapie is found to be a risk to humans, in determining appropriate Specified Risk Material controls. The current lack of sufficient material for studies was noted.
32. Question 15 asked what experimental or surveillance results would be required for the committee to conclude that a human TSE was associated with the consumption of atypical scrapie infected material. Members agreed that this would be difficult to answer. However, as for BSE, the emergence of a new type of CJD which shows the same transmission characteristics as atypical scrapie in non-human primates and mice would provide a strong indication.
33. Question 16 asked what negative experimental or surveillance results would be needed to conclude atypical scrapie was not a risk. Members concluded that negative results are very hard to interpret, however negative results from current and retrospective surveillance and transmission studies would be suggestive of a negligible risk.
34. In summary, the Chair concluded it was difficult to assess changes to understanding of the human health risk of atypical scrapie in the absence of hard scientific data, and that no one data set on its own was likely to be definitive. Studies comparing the properties of atypical scrapie and other TSE agents using the same animal model, especially humanised mice or non-human primates, would be most informative in the short term. Surveillance data to assess any association between forms of CJD and atypical scrapie prevalence would be most persuasive but are unlikely to become available in the short term. In assessing the risk it would be important to consider all the information available, rather than data from single studies considered in isolation.

ITEM 6 FATEPRIDE (SEAC 97/4)

35. The Chair explained that FATEPRIDE is a multi-centre European Union funded project that examined the possible influence of environmental trace elements on the occurrence of TSEs.
36. Professor David Brown (University of Bath) explained that the project had principally studied potential interactions between prion disease and copper and manganese, although interactions with other environmental factors such as organophosphates had also been assessed. No link, other than with manganese, between many environmental factors studied, including organophosphates, and TSEs was found. The key experiments and findings had been summarised in SEAC paper 97/4. The main conclusions were that manganese binds to PrP with similar affinity to known manganese binding proteins, induces conformational change in PrP, catalyses PrP aggregation, induces protease resistance in PrP, increases PrP expression levels and increases cellular susceptibility to prion infection. Manganese had also been found at high levels on farms with a high classical scrapie incidence and manganese was found to increase the stability of PrP in soil. Although it had been the intention to create maps of bioavailable manganese and compare those to similar maps of TSE hotspots, this had not been possible as no data of sufficient precision relating the location of BSE or scrapie cases was made available. Further studies were required to investigate the interactions of manganese and prions.
37. Members noted that the study suggested an association between high levels of bioavailable manganese, low levels of bioavailable copper and classical scrapie in field studies. However, it was likely that other factors such as soil pH and organic matter may also be involved. It was acknowledged that it was very difficult in environmental studies to exclude potential confounding factors. The experimental and field data suggested that manganese may influence the susceptibility to TSEs. However, there was no evidence that environmental factors, including manganese, cause disease.
38. Members noted that data on BSE should allow spatial mapping of cases, however sheep movements were so complex that it is not possible to create similar maps for classical or atypical scrapie.
39. Members suggested that further research could investigate the differential stability of a range of TSE agents bound with manganese in soil, although other modifying factors in soil such as

soil content and pH are likely. In addition, further animal studies could examine the effect of manganese on a range of TSE agents.

ITEM 7 – UPDATE ON SUBCLINICAL vCJD PREVALENCE STUDIES

40. Professor Noel Gill (Health Protection Agency [HPA]) explained that the National Anonymous Tonsil Archive was on track to report to the SEAC Epidemiology Subgroup in June 2007 the analysis of tonsils collected to date from the age group likely to be at most risk of BSE infection. The report from the Post Mortem Tissue Archive Working Group investigating the feasibility of a large scale archive of tissues collected from coroners' autopsies would be published in the near future. The recommendations would be considered by the Department of Health (DH). The HPA had received four tenders from manufacturers of prototype blood tests for the analysis of a large number of anonymised blood samples. These tenders would be considered by the HPA's Tissue Testing Advisory Group at the end of May 2007 and the study would be taken forward on the advice of this group.
41. Members asked whether there were sufficient blood samples from vCJD cases to include as controls in a survey of anonymised blood samples. Professor Gill noted that such material was in very short supply and access was considered by an advisory group convened by the National Institute of Biological Standards and Control (NIBSC). A member noted that blood from vCJD cases held at the NCJDSU had been sent to NIBSC and that other institutes had agreed to provide the samples that they hold to NIBSC. A suggestion had been made that the current protocol for collection of blood from vCJD cases be altered so that future blood samples can be sent directly to NIBSC.

ITEM 8 – FUTURE ASSESSMENT OF LIKELY vCJD INFECTIVITY ASSOCIATED WITH PLASMA PRODUCTS (SEAC 97/5)

42. Dr Peter Bennett (DH) explained that, although there was some consensus about the risk of vCJD transmission from transfusion of blood components, there was little consensus about the risks from transfusion of plasma products. Although, since 1999, plasma products were produced from plasma imported from countries considered to be free of BSE, a risk of infection existed for individuals transfused with plasma products prior to this time. Thus, there is a need to quantify the effect of the production process prior to 1999 on the levels of infectivity in plasma products produced from contaminated plasma. Studies to examine the effect of the production process had mostly used plasma spiked

with TSE agents. As SEAC had considered spiking studies to be of uncertain reliability in the past, these data had been ignored. However, more recently SEAC had considered spiking studies useful in assessing the efficacy of prion reduction filters, provided confirmatory experiments were conducted using endogenous infectivity. Given this, a reassessment of the data on the effect of plasma product production may be informative. In addition, SEAC consideration of the time window for possible infections arising from use of plasma products prior to 1999 would also be helpful.

43. The Chair agreed that SEAC should consider these issues at SEAC 98. Members noted that it is unlikely that new compelling data would be available to inform such a reassessment. An assessment is complicated by the variability in the likely distribution of infectivity in plasma components and in the effect of processing steps. It was suggested that some new data may be available from the Haemophilia Doctors Association and that a representative should be invited for the discussion. It was also suggested that a representative from Bio Products Laboratory, the main centre for plasma fractionation in the UK, be invited.
44. The Chair closed the meeting, thanking all those that had presented information to the committee and all those that attended the meeting.

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