

### SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Minutes of the 102<sup>nd</sup> meeting held on 4<sup>th</sup> March 2009  
Nobel House, 17 Smith Square, London SW1P 3JR

Members:	Professor C. Higgins (Chair) Professor A. Ghani Mr. P. Jinman (Deputy Chair) Professor R. Knight Ms. D. McCrea Professor G. Medley Professor J. Nicoll Dr. R. Salmon Professor A. Williams
Assessors:	Mr. J. Bourne (Defra) Dr. A. Douglas (AFBINI) Dr. S. Hayes (NAW) Mr. M. Noterman (DH) Dr. A. Riley (SG)
Technical Experts:	Mr. P. Burke (Defra) Professor N. Gill (HPA) Dr. I. Hill (FSA) Dr. J. Hope (VLA)
Secretary:	Dr. P. Grimley
Secretariat:	Dr. T. Barlow Dr. B. Cole Dr. D. Cutts Dr. A. Patey
Also in attendance	Mr. S. Dobra (DH) Dr. M. Jeffrey (VLA)

## **ITEM 1 – INTRODUCTION**

1. The Chair welcomed everyone to the 102<sup>nd</sup> meeting of SEAC. He explained that, in accordance with the SEAC Code of Practice, there would be a reserved business session in the afternoon to discuss preliminary unpublished data. Short summaries of all the discussions would be published on the SEAC website.
2. The 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. Meetings would be held in government buildings where possible, for reasons of cost. This would not compromise the committee's independence and meetings would still be open to the public. Government officials with responsibility for transmissible spongiform encephalopathy (TSE) policy may be invited to contribute to discussions.
3. Members were reminded that they are obliged to declare any commercial or other interests they may have at the relevant agenda items. Members were asked 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.
4. Apologies for absence had been received from Professors John Collinge, Corinne Lasmezas and Jean Manson. Professor Margaret Stanley would attend the reserved business session.
5. The next SEAC meeting was scheduled for 10<sup>th</sup> June 2009 at a venue to be confirmed.

## **ITEM 2 – APPROVAL OF MINUTES FROM SEAC 101 (SEAC 102/1)**

6. The minutes of SEAC 101 were agreed as a correct record.

## **ITEM 3 – CURRENT ISSUES**

7. There were no current issues to discuss, other than to note a recent report of a possible clinical case of variant Creutzfeldt-Jakob Disease (vCJD) of methionine (M) / valine (V) genotype at codon 129 of the prion protein gene that would be discussed under item 6.

#### ITEM 4 – UPDATE ON ANIMAL TSEs

8. Mr Patrick Burke (Defra) presented an update on the results of surveillance of BSE in cattle, of classical and atypical scrapie in sheep and of TSEs in deer. In the UK, over 183 000 BSE cases have been detected since 1988. The BSE epidemic in cattle peaked in 1992, with over 37 000 confirmed cases, and has since progressively declined with 35 cases confirmed by active, and two by passive, surveillance in 2008. Four of these cases were animals slaughtered for human consumption, although they did not enter the food chain. Estimates showed a decreasing exponential trend in the prevalence of BSE infection in successive birth cohorts born after 1996.
9. Mr Burke explained that the number of cases of classical scrapie found by passive surveillance continued to decline. Active surveillance of sheep over 18 months of age showed that the incidence rate of classical scrapie declined from 0.19% in 2005 to below 0.03% in 2008. Atypical scrapie in sheep was detected mostly by active surveillance. No cases of atypical scrapie were detected by passive surveillance in 2008 compared with eight cases found between 2005 and 2007. Active surveillance of sheep over 18 months of age showed that the incidence rate of atypical scrapie had remained relatively constant at around 0.07%. Mr Burke highlighted the conclusions of two recent publications. McIntyre *et al.*<sup>1</sup> had shown that the estimated prevalence in atypical scrapie was similar in both abattoir and fallen stock surveys and that there were no temporal trends in the prevalence of atypical scrapie in British sheep between 2002 and 2006. Fediaevsky *et al.*<sup>2</sup> had shown that prevalence estimates of classical scrapie in Europe were more variable than those for atypical scrapie, which appeared relatively homogeneous across countries, surveillance streams and calendar years of surveillance.
10. Mr Burke explained that a recent EU survey involved testing over 10 000 deer for TSEs, including 601 wild and an equal number of farmed red deer in the UK. The survey had found no TSE positive animals.
11. The Chair asked if the decrease in classical scrapie incidence was in line with that predicted for the National Scrapie Plan genotyping scheme. Mr Burke replied that it was difficult to determine

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<sup>1</sup> McIntyre *et al.* (2008) No temporal trends in the prevalence of atypical scrapie in British sheep. *BMC Vet. Res.* 4, 13.

<sup>2</sup> Fediaevsky *et al.* A descriptive study of the prevalence of atypical scrapie and classical scrapie in sheep in 20 European countries. *BMC Vet. Res.* 4:19

whether the effect was due to the Ram Genotyping Scheme or the Compulsory Scrapie Flock Scheme or a combination of the two<sup>3</sup>. The Chair suggested that the success of these schemes in reducing classical scrapie should be highlighted.

12. The Chair also suggested that it may not be possible to ever fully eradicate BSE and that it is important for Defra to communicate that possibility.
13. Members noted that very few of the red deer tested for TSEs were fallen or sick animals, particularly amongst the wild deer tested. It may be more appropriate to test sick animals to find TSEs, if they are present. Mr Burke explained that samples from sick animals were difficult to obtain particularly in the wild deer population. Members noted that the small size of the survey made it difficult to reach conclusions on the presence, or not, of TSEs in deer.

#### **ITEM 5 – NEW RESULTS ON IDIOPATHIC BRAINSTEM NEURONAL CHROMATOLYSIS (IBNC) FROM THE VETERINARY LABORATORIES AGENCY (VLA)**

14. Dr Martin Jeffrey (Veterinary Laboratories Agency (VLA)) presented an overview of a recent publication on Idiopathic Brainstem Neuronal Chromatolysis (IBNC)<sup>4</sup>. During the period 1987 to 1992, VLA examined the neuropathology of whole brains from all submissions made under the BSE orders in Scotland to look for possible strain variation or mutation of the existing BSE strain or other prion diseases of cattle. During the course of these investigations a small number of cases of IBNC were identified. Abnormally accumulated prion protein was found in the brains of the IBNC cases. Dr Jeffrey suggested that these findings indicate that the range of prion disease pathology may be wider than thought or that abnormalities of prion protein gene expression might be associated with brain lesions unconnected with classical prion diseases.
15. A member noted that IBNC appears to be a rare disease and the prevalence of IBNC seems not to have increased over time. Dr Jeffrey noted that the detection rate of IBNC is dependent on the design of cattle surveillance and it is possible that cases of IBNC may be missed by current surveillance. Nevertheless, it is likely that IBNC is rare. A member suggested that should transmission

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<sup>3</sup> Truscott, J.E. and Ferguson, N. M. (2008) Control of scrapie in the UK sheep population. *Epidemiology and Infection*, 8 August 2008, on-line, doi: 10.1017/S0950268808001064.

<sup>4</sup> Jeffrey *et al.* (2008) Idiopathic Brainstem Neuronal Chromatolysis (IBNC): a novel prion protein related disorder of cattle? 4, 38.

experiments using bovinised, ovinised and humanised mice indicate that IBNC is transmissible, the ability of surveillance to detect IBNC should be examined. It would be important to conduct transmission experiments using brains from IBNC cases proven, as far as possible, not to have BSE.

16. A member asked about whether differential diagnosis was made on BSE suspect cases that subsequently were found not to be BSE. Dr Yvonne Boyd (Defra) noted that currently less than 10% of suspected BSE suspect cases were subsequently confirmed. Defra was funding a research project to examine a number of clinical BSE suspects subsequently found not to be BSE, but routine differential diagnosis was not carried out on all such cases. Dr Jim Hope (VLA) added that such cases were not specifically investigated for the presence of other neurological diseases; only the presence of spongiform change and the properties of the prion protein were assessed. However, obvious differential diagnoses were reported, e.g. meningoencephalitis, if detected.
17. A member noted that even though prion protein accumulation was evident in IBNC cases, the form of prion protein produced was protease sensitive, indicating that IBNC may not be a form of TSE. Dr Jeffrey explained that, from the biochemical studies conducted, an abnormally folded, but protease sensitive, form of prion protein could not be ruled out.
18. A member asked if any of the cases of IBNC examined showed evidence of possible co-infection with classical BSE. Dr Jeffrey replied that as the neuropathological lesions of IBNC and BSE differed, co-infection should be detectable. However, no evidence of co-infection had been detected. A member suggested it may be possible to re-examine archived BSE brains for the possibility of IBNC co-infection to establish whether IBNC is indeed a rare disease. Dr Jeffrey noted that as IBNC predominantly affects older cattle, the age of the cattle brains would be a factor in such an investigation.
19. A member asked if the sequence of the prion protein gene had been studied in the IBNC cases as this can influence the pathogenesis and neuropathology of prion diseases. Dr Jeffrey replied that no detailed studies had been conducted.
20. A member noted that IBNC appeared to be a neurological condition and therefore the specified risk material controls would confer public health protection should IBNC be zoonotic.

21. The Chair summarised the discussion, noting that IBNC appears to pose no immediate high risk to human health. It appears to be a rare disease, although current surveillance may miss cases. It cannot be concluded if IBNC is transmissible, or not. Transmission studies using material from IBNC cases proven not to be BSE, that include transgenic mice lines, are important. Studies to investigate whether IBNC is associated with a normal or abnormal form of prion protein could be informative.

## **ITEM 6 – UPDATE ON CJD EPIDEMIOLOGY**

22. Professor Richard Knight (National CJD Surveillance Unit) updated SEAC on the latest figures for the number of clinical vCJD and sporadic CJD (sCJD) cases. To date there had been 168 definite and probable clinical cases of vCJD in the UK - 165 from dietary infection with BSE and three from vCJD infection via blood transfusion. Four cases are still alive. The number of deaths from vCJD peaked at 28 in 2000 and had since declined with one known death in 2008. The trend in incidence of vCJD deaths fits the quadratic-exponential model. The median age of death is 28 years of age. No individuals born after 1989 have developed vCJD to date. Analysis of vCJD deaths by birth cohort supports the hypothesis that susceptibility to vCJD from dietary exposure to BSE may be age-related with a peak in susceptibility between five and 20 years of age.
23. Professor Knight explained that all the clinical vCJD cases genotyped to date were of the MM genotype with the exception of one case of the MV genotype recently classified as possible vCJD. This patient had died. Although the clinical features in life suggested this was a case of vCJD, it had not been possible to undertake a tonsil biopsy in life or neuropathological examination post mortem so the diagnosis could not be confirmed. The patient was born in 1978, with disease onset in 2007 and death in 2009. The clinical profile of this MV case was consistent with that observed for MM cases suggesting that the neuropathological profile of vCJD in MV and MM cases may be similar.
24. Professor Knight noted that four vCJD patients had been treated with intra-ventricular pentosan polysulphate (PPS) in the UK, in addition to one sCJD, two Gerstmann-Sträussler-Scheinker (GSS) disease and one human growth hormone (hGH) case. There is no evidence of benefit from the use of PPS for the sCJD, GSS and hGH cases. However, it appears PPS may have significantly prolonged the clinical phase of the illness in the vCJD cases

treated, although no significant improvement in the clinical condition of these patients had been observed.

25. Professor Knight explained that elsewhere in the world 44 clinical vCJD cases had been reported with 23 in France, five in Spain, four in the Republic of Ireland, three in each of the USA and the Netherlands, two in Portugal and single cases in Canada, Saudi Arabia, Italy and Japan. Infection was presumed to have occurred in the UK in respect of two Irish and two USA cases, one French case, one Japanese case and one Canadian case. The time of the peak of onset of vCJD was five years later in non-UK countries than in the UK.
26. Professor Knight summarised studies to examine potential blood-borne exposures to vCJD. The Transfusion Medicine Epidemiology Review (TMER) identified 66 patients as recipients of labile blood components from donors whom later developed vCJD. Forty three of those patients had died due to non-vCJD related illnesses but three recipients developed clinical vCJD and one subclinical vCJD infections. The reverse TMER study identified three vCJD cases as receiving blood from vCJD infected donors. A study of plasma donations prepared from 1986 to 1998 plasma had identified 25 units of plasma prepared from donations from 11 individuals who later developed vCJD.
27. Professor Knight summarised data on sCJD cases. From May 1990 to January 2009, 1027 cases of sCJD had been identified in the UK with a mean age at death of 67 years and genotype distribution of 63% MM, 19% MV and 18% VV at codon 129 of the prion protein gene.
28. Members asked in what circumstances an autopsy is legally required. Professor Knight explained that autopsy may be legally required when the cause of death is considered not to be from natural causes or is unknown. However, the wishes of the family of the deceased are also considered.
29. Dr Elaine Gadd (Department of Health (DH)) asked about the clinical state of the vCJD cases treated with PPS. Professor Knight explained that the neurological impairment of the patients when treatment began was so advanced that any subtle changes in clinical state would be difficult to assess objectively. The condition of two patients is considered to have significantly deteriorated, whilst one patient may have improved slightly.

## **ITEM 7 – COMPARING THE RELATIVE RISK OF vCJD TRANSMISSION VIA SINGLE UNIT AND POOLED PLASMA FROM UK AND NON-UK SOURCES (SEAC 102/3)**

30. Mr Stephen Dobra (DH) presented an overview of the risk assessment that had been developed by the Department of Health. He explained that there are three Fresh Frozen Plasma (FFP) products in use in the UK: (i) single unit FFP from UK donors given to recipients over 16 years of age, (ii) single unit methylene-blue treated FFP sourced from donors in the United States of America and given to patients under 16 years of age, and (iii) solvent detergent treated FFP (SD FFP) manufactured from pooled plasma currently sourced from countries with no known vCJD cases (although some, such as Germany, have a known BSE risk) given to patients with Thrombotic Thrombocytopenic Purpura (TTP). As most FFP is sourced from UK donors, there is a potential risk of vCJD transmission from its use. Prion reduction technologies may be available in the future for pooled SD FFP.
31. Mr Dobra explained that the risk assessment had been prepared to support decision making by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) which is considering options for extending the use of imported plasma to all recipients and National Health Service Blood and Transplant which is considering the procurement of plasma from alternative source countries. The risk assessment examines the relative residual risk from use of plasma taking into account the source country, whether it is single unit or pooled, and the method of processing. SEAC was being asked to review the methodology used for the sourcing and pooling elements of the risk assessment. DH will convene an expert group to assess the impact of processing taking into account previous SEAC advice.
32. Members suggested that the presentation of the risk assessment could be improved to provide greater clarity on the reasoning behind some of the assumptions made.
33. A member asked about the estimation of the probability that infectivity would be carried by a plasma product from pooled plasma donations that had been contaminated by a donor infected with vCJD. Mr Dobra suggested that in low infectivity scenarios, infectivity might not be present in all of the plasma product units produced from a contaminated pool as there may be an uneven distribution of infectivity throughout the pool. Members noted that the physico-chemical nature of infectivity in plasma is not known. It may be homogeneously spread within the pool or remain in the

form of discrete entities spread unevenly, or something between these two extremes. There may be no low dose threshold for infection.

34. Members asked what confidence there may be in the results from the risk assessment given the large number of variables with large uncertainties. It was noted that as the relative risks (as opposed to absolute risks) posed by plasma products were being estimated, assumptions around the timing, level and distribution of infectivity in blood where there is much uncertainty would not appreciably affect the estimations made. The best way to manage other assumptions where there is large uncertainty, such as around the prevalence of vCJD in the UK and other countries, would be to develop a range of scenarios incorporating reasonable high and low value estimates for such parameters. It was noted that some patients received a large number of transfusions of plasma and plasma products. It may be possible to rule out some scenarios on the basis of observations made on these groups of patients. Members reiterated the importance SEAC placed on obtaining better estimates for the prevalence of subclinical vCJD through a post mortem tissue archive.
35. A member suggested that experiments to examine the infectivity of unused batches of plasma products might provide useful data. It was considered that such experiments may be difficult to conduct as there may be a small number of contaminated batches and they would be difficult to identify.
36. A member asked why prion reduction technologies would only be applied to pooled plasma. Mr Dobra explained that the only proposal of which he was aware had been developed by a manufacturer of pooled plasma and involved filtering a large volume of plasma through a column. The Chair remarked on the lack of independent validation of the efficacy of prion reduction filters to date.
37. A member asked whether the risk assessment could take into account the measures taken in different countries to prevent dietary exposure to BSE and the movement of people from other countries to the UK during the BSE epidemic. Mr Dobra explained that there are no consistent data available to assess differences in dietary exposure to BSE in different European countries. Most countries excluded from donating blood anyone who had visited or been resident in the UK for a significant period of time.

38. A member noted that the risk of vCJD transmission alters depending on the age of the blood donor and asked whether restrictions on the age of donation could be introduced to manage the vCJD transmission risks. Mr Dobra explained that this was possible but would require clear advice from SEAC on the difference in risk and was complicated by the need to ensure sufficient supplies of blood.
39. The Chair summarised the discussion, noting that the committee felt that the best way of handling the uncertainties around key assumptions made in the risk assessment is to use reasonable high and low values for each parameter to derive a range of scenarios. Scenarios could be validated against the number of infections observed in populations that had received large numbers of transfusions of plasma products.

#### **ITEM 8 – ANY OTHER BUSINESS**

40. There was no other business. The Chair closed the open meeting, thanking all those who had presented information to the committee and all who attended the meeting.