

### SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Minutes of the 103<sup>rd</sup> Meeting held on 24<sup>th</sup> November 2009  
at Nobel House, 17 Smith Square, London SW1P 3JR.

Members:	Professor C. Higgins (Chair) Professor J. Collinge Professor A. Ghani Mr. P. Jinman (Deputy Chair) Professor R. Knight Professor J. Manson Ms. D. McCrea Professor G. Medley Professor J. Nicoll Dr. R. Salmon Professor A. Williams
Assessors:	Dr. E. Redmond (FSA) Mr. M. Noterman (DH)
Technical Experts:	Dr. P. Bennett (DH) Mr. P. Burke (Defra) Dr J Clewley (HPA) Miss A. Conroy (FSA) Dr. M. Dawson (VLA) Dr. I. Hill (FSA)
Secretary:	Dr. P. Grimley
Secretariat:	Dr. B Cole Dr. D. Cutts Dr. A. Patey
Also in attendance	Dr. A. Adkin (VLA)

## **ITEM 1 – INTRODUCTION**

1. As the Chair had been delayed by a transport problem, the Deputy Chair welcomed everyone to the 103<sup>rd</sup> Meeting of SEAC. He explained that, in accordance with the SEAC Code of Practice, there would be a short Reserved Business Session, after the Open Business Session, to discuss preliminary unpublished data. Short summaries of all the discussions at the Open Business Session would be published within a few days 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. 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, generally within three months.
4. The only Committee Member not present was Professor Margaret Stanley who had sent apologies for her absence.

## **ITEM 2 – APPROVAL OF MINUTES FROM SEAC 102 (SEAC 103/1)**

5. The minutes of SEAC 102 were agreed as a correct record after one change, namely in paragraph 16 (last line), where “meningoencephalitis” should be replaced by “meningoencephalitis”.

## **ITEM 3 – CURRENT ISSUES**

6. SEAC was updated on the Strain Typing Expert Group report on a suspected BSE case in a historic Scottish goat. The goat had originally been diagnosed with scrapie in 1990. However, retrospective tests have now confirmed that the goat isolate was indistinguishable from BSE. The results do not affect the SEAC position statement on the Potential Human Health Risks from Changes to Classical Scrapie Controls published in February 2008. That statement concluded that if BSE was confirmed, the fact that

the animal was born prior to the introduction of the ruminant feed ban meant it could have been exposed to BSE contaminated feed.

7. Atypical scrapie has been confirmed in a sheep from the New Zealand (NZ) national flock. NZ authorities have stated that because atypical scrapie is distinct from classical scrapie, they consider that NZ remains “free from scrapie.” The Chair, who had now joined the Meeting, noted that in light of the identification of atypical scrapie in NZ sourced sheep in the Arthur Rickwood flock this result was not unexpected. The Chair reminded Members that there was still no evidence that atypical scrapie could be transmitted to humans.
8. The Advisory Committee on the Safety of Blood, Tissues and Organs has recommended that blood prion filtration should be used to treat patients with no prior evidence of dietary exposure to BSE. SEAC noted that the Department of Health Ministers were currently considering this recommendation.
9. Members were informed of a recent study<sup>1</sup> published into genetic resistance to kuru discovered in a small population in Papua New Guinea. Those determined to exhibit resistance were found to have a glycine to valine substitution of the prion protein gene at residue 127. It is concluded that the frequency of the mutation increased by “natural selection” as the population lies at the epicentre of the disease area. The observed resistance to disease is unique to this area and has not been found in patients with kuru or in unexposed population groups worldwide.
10. In light of the recent high profile dismissal of a Government scientific advisor, the Chair said he would be concerned if any member of a Scientific Advisory Committee (SAC) were to be dismissed for expressing scientific opinions whether or not these contradict Government policy. It was added that SEAC adheres to the principles of the Philips’ report and clearly recognises the distinction between risk management and risk assessment: this distinction may not be so clearly defined in the work of other SACs. The Chair said that there was to be a meeting of scientists engaged in work on government committees and that Professor Graham Medley would be representing SEAC.

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<sup>1</sup> A Novel Protective Prion Protein Variant that Colocalizes with Kuru Exposure by S Mead, J Whitfield, M Poulter, P Shah, J Uphill, T Campbell, H Al-Dujaily, H Hummerich, J Beck, C A Mein, C Verzilli, J Whittaker, M P Alpers & J Collinge. *New Eng J Med.*, 2009, **361**, 2056-65.

## ITEM 4 – UPDATE ON CJD EPIDEMIOLOGY

11. Professor Richard Knight (National CJD Surveillance Unit) provided the Committee with the latest figures for the number of clinical vCJD and sporadic CJD (sCJD) cases. To date there had been 170 definite or probable clinical cases of vCJD in the UK - 167 from probable dietary infection with BSE and three from probable vCJD infection via transfusion of blood from donors who later developed vCJD. Of the 150 cases tested all were codon 129MM. Four cases are still alive. The number of deaths from vCJD peaked at 28 in 2000 and had since declined with two known deaths so far in 2009. The median age of death is 30 years of age.
12. Professor Knight explained that elsewhere in the world 47 clinical vCJD cases have been reported with 25 in France, five in Spain, four in the Republic of Ireland, three in both the USA and the Netherlands, two in Portugal and Italy and single cases in Canada, Saudi Arabia 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.
13. Professor Knight explained that one MV genotype case had been classified as possible vCJD as clinical features were consistent with the disease. However, it had not been possible to undertake neuropathological examination post mortem so the diagnosis could not be confirmed. The clinical profile of this MV case was consistent with that observed for MM cases.
14. Professor Knight summarised data on sCJD cases stating that from May 1990 to September 2009, 1080 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.
15. Professor Knight also provided a brief report on the novel human disease known as Protease-Sensitive Prionopathy (PSP<sup>r</sup>). The initial eleven cases described by Gambetti<sup>2</sup> exhibited a mean age of onset of 62 years and mean disease duration of 20 months. Eight out of ten had a family history of dementia and were codon 129VV. Cases had minimal spongiform change and minimal immunohistochemical stained PrP deposits with distinct patterns in the cortex and cerebellum. Western Blot (WB) also shows a minimal amount of PrP<sup>res</sup> present. Further studies by Gambetti

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<sup>2</sup> A Novel Human Disease with Abnormal Prion Protein Sensitive Protease. Gambetti, P., Dong, Z., Yuan, J., Xiao, X., et al. *Ann Neurol* 2008;63:697-708.

have now identified codon 129MV and MM cases which have a longer disease duration and exhibit some PK resistance. The cases did not have clinical profiles typical for sCJD. A UK case and a Dutch case have also been identified, with characteristics not inconsistent with the Gambetti studies.

16. Professor Knight added that due to the unique clinical presentation of the disease it was likely that at least some cases of disease would not be identified for referral, making it hard to obtain complete data on this disease. However, it was likely that a case would be identified as a prion disease at autopsy and the WB currently used would be able to identify the unique profile which categorises this disease. A retrospective review of the NCJDSU brain bank is underway to look for more cases.
17. A Member asked whether the recent review of neuropathology archives in the UK would have identified PSP<sup>r</sup>. Professor Knight responded that it would be dependent on the type of WB used at the time which is currently not known. The use of appropriate WB methodology would be an issue in accurately identifying the relevant characteristics.
18. One Member was not convinced by the characterisation of this disease, adding that clinical cases classified as Alzheimer's Disease have shown similar laddering profiles in WB, protease resistant fragments and the presence of abnormal PrP. The disease has, to date, not been shown to be transmissible which means it should not yet be categorised a prion disease under the current terminology.
19. Summing up, the Chair noted that it was clear that more information was required to fully characterise and fill knowledge gaps regarding this disease. It was important that its unique pathology be more widely recognised to enable future diagnosis and enable tissue collection during autopsy procedures. SEAC will keep a watching brief on emerging data which may characterise the disease further.

## **ITEM 5 – EFFECT OF AGE ON THE PATHOGENESIS OF TSEs (SEAC 103/2)**

20. The Committee discussed a recent paper<sup>3</sup> on the effect of host age on the pathogenesis of TSEs, which was published in September

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<sup>3</sup> The effects of host age on follicular dendritic cell status dramatically impair scrapie agent neuroinvasion in aged mice. K L Brown, G J Wathne, J Sales, M E Bruce, and N A Mabbott, the Journal of Immunology 2009, doi:10.4049/jimmunol.0802695.

2009. This study finds that early TSE agent accumulation in the spleens of aged mice was significantly impaired compared to that in young adults. Furthermore, following peripheral exposure, none of the aged mice developed clinical TSE disease during their life spans, although most mice displayed histopathological signs of TSE disease in their brains. Comparison of follicular dendritic cell networks (FDCs) in the spleens of aged and young adult mice, showed a highly significant reduction in the total number of PrP<sup>C</sup> expressing FDCs in aged mice when compared with those of young adults. The data imply that the reduced status of FDCs in aged mice significantly impairs the early TSE agent accumulation in lymphoid tissues and subsequent neuroinvasion. Furthermore, the inefficient neuroinvasion in aged individuals may lead to significant levels of subclinical TSE disease in the population.

21. The Committee agreed that a competent immune system was required for efficient replication of TSEs in the host. A Member suggested that there might be other interpretations of this result and asked if other types of cell within the immune system were being investigated. It was confirmed that this work is in progress. Members noted that older people are more immuno-compromised than the young. A Member also noted that a question which remains unanswered is why (comparing the UK and France) the age range for onset of vCJD has been so precise over the duration of the epidemic. The Committee concluded that there are insufficient data to conclude that the results in the paper provided an explanation for the young age of vCJD patients.

## **ITEM 6 – UP-DATE ON vCJD PREVALENCE STUDIES**

22. Dr Jonathan Clewley (HPA) updated the Committee on progress with vCJD prevalence studies. To date, the National Anonymous Tonsil Archive (NATA) has tested approximately 80,000 pairs of tonsils, of which approximately 16,000 are in the 1961-1985 birth cohort. None were positive. The Institute of Neurology is undertaking IHC analysis of 10,075 samples, including all those in the 1961-1985 birth cohort and any that produced equivocal results by EIA. One of these samples has shown one positive follicle in one section by IHC, but other sections and two other blocks were negative by IHC. The finding will be discussed at the NATA Expert Advisory Group (EAG) meeting on 9 December 2009, which will report to the Department of Health, and then inform SEAC.

23. Pilot studies for a new study of 30,000 appendices, to be tested by immunohistochemistry, are underway. The full study will start in early 2010, and results are due in 2012.
24. A pilot for a study of spleens obtained from post mortems will also start in early 2010. The pilot, which will be based in four centres and give access to a potential 900 tissue samples, will be used to assess four different methodologies for delivering the study, involving coroners, NHS bereavement services and the NHS Blood and Transplant tissue service. A report on the efficacy of those methodologies will be made in June 2010, to inform decisions on rolling the study out more widely.
25. The Chair asked whether any analysis has been done of the number of samples needed in order to be able to either confirm or revise the current prevalence estimate provided by the Hilton data (1:4,000). A Member suggested that in order to have sufficient power, a study would have to test approximately 50,000 samples. The Chair suggested that this issue needed to be considered before the studies started, and if sufficient tissue samples cannot be obtained there would be no point in starting the study.
26. A Member reminded the committee that there is still the issue of comparing results from different tissues, which was discussed at SEAC 102.
27. The Chair also suggested that calculations needed to be done to ascertain when to stop testing tonsil samples. Dr Clewley stated that a figure of 100,000 had initially been agreed because it would have sufficient statistical power to answer the question.
28. A Member asked if the meeting of the EAG on 9 December would establish a set of criteria by which to define false positives, or whether each case would have to be explored in a different manner. Dr Clewley confirmed that the anomalous IHC finding in a NATA tonsil would be considered separately. The definition of a positive, in terms of a specific WB band pattern and IHC staining, has already been established, but the tonsil sample does not meet those criteria. A question for the EAG would be how to use the remaining tissue.

## ITEM 7<sup>4</sup> – CATEGORY 3 ANIMAL PRODUCTS IN FERTILISERS (SEAC 103/3)

29. The Chair reminded Members that in 2005 the Committee had considered a release assessment which evaluated the amount of potential infectivity available in the soil of non-pasture land following the application of Category 3-derived<sup>5</sup> fertiliser. European Regulations are now being renegotiated and Defra are considering whether it is appropriate to seek a relaxation of rendering requirements (see paper 103/3). In order to inform this consideration, Defra commissioned a full Risk Assessment (RA) which was completed in 2008 which SEAC is now invited to consider.
30. Dr Amie Adkin (VLA) said that the main changes compared to the previous RA reviewed by SEAC were: **firstly**, that the values assigned to parameters have been amended to take account of any increase in scientific knowledge, legislative changes and the decline in disease incidence over time; **secondly**, that account is taken of a case study investigating the palatability to ruminants of fertilisers applied to land; and **thirdly**, that the assessment has been extended with an exposure assessment and dose response model.
31. The effects of each of the seven processing methods on TSE infectivity are not known, with the exception of experimental data regarding “Method 1”. Owing to the absence of such information, the RA compares two scenarios based on the use of the processing methods at opposite ends of the range permitted in legislation: “Method 1” and “Method 7”. Under “Method 7” it is assumed that there is no decay of the abnormal prion protein.
32. The RA concludes that the number of animals infected with a TSE disease annually, owing to exposure to fertilizer produced from Category 3 animal by-products according to “Method 1”, is low (i.e. below one). Indeed, there is 90% certainty that the maximum number would be one new infection. When considering fertiliser produced by “Method 7” the estimated mean number of new BSE infections in cattle is 1.1, the number of new infections of scrapie is 47 and the number of new infections of sheep BSE is 0.04.

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<sup>4</sup> After the meeting the Member who initiated the discussion (see paragraphs 33 & 35) provided the Secretariat with written notes which described in more detail the points made in discussion. These were circulated to the other Members of the Committee and no disagreement was registered. The Secretariat has used sections of these notes to produce more detail of the Committee’s consideration of the RA.

<sup>5</sup> Category 3 is low risk material, most of which is fit for human consumption, but not intended for human consumption.

33. A Member said that the methodology used in the RA was scientifically valid. However, the RA aimed to estimate the number of livestock that are infected with TSE in one year following the application of fertilizer for one year only. A better approach would be to consider the continued application of fertilizer over a number of years, and to include the decay of infectivity in the fertilizer with time. Infectivity would be expected to increase to a plateau determined by the relationship between the application and decay rates. However, at the time of completion of the RA there was little information on decay rates of applied fertilizer, apart from some evidence that it is very slow; it is also known to depend on soil type, climate and many other factors, which would increase the heterogeneity of the outcome.
34. Dr Adkin said that including temporal aspects into the RA had been considered: however, for BSE in cattle, the probability that two separately contaminated fertiliser batches would be applied to the same field was low and further decreasing over time. The situation was different for scrapie because of the greater number of infected animals, and therefore potential infectivity in derived fertiliser. However, temporal aspects were not considered in the RA because the relevant information on the behaviour of TSEs in soil was not available when the RA was completed, and indeed there is still much scientific uncertainty regarding TSE decay in soils. Regarding the purchase of fertiliser for use on farm, a Member said that a farmer might buy at a good price an amount sufficient for a period of time, so that the assumption that application would be confined to a single year might be erroneous.
35. A Member said that an assumption in the RA was that only Category 3 material would be applied to non-pasture land. However the RA should include the possibility of Regulatory failure and Category 1 and 2 materials<sup>6</sup> might occasionally (by accident) and potentially systematically be included in fertilisers.
36. A Member raised the question as to whether fertiliser sourced from outside the UK could provide a route of transmission from ruminant to ruminant that might be capable of supporting an epidemic and said that the RA should have included the possibility that fertilisers were sourced from outside the UK. Mr Burke (Defra) said that he

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<sup>6</sup> Categories 1 & 2 are the highest risk materials, animals with a suspected or confirmed TSE, Specified Risk Material, condemned meat, diseased animals etc.

understood that currently there was very little meat and bone meal used as fertiliser on non-arable land in the UK.

37. Another Member added that there has been a considerable reduction in TSE over the past two decades, and BSE in cattle is close to being eliminated from the UK. This has been achieved through the comprehensive regulation of the use of animal by-products which has been a key element of the Government's strategy to address the disease. The risks associated with any relaxation of Regulatory controls should therefore be very carefully considered before any decision is made.
38. Answering further points made by Members, Dr Adkin said that the RA did assume SRM controls were not 100% effective with some contamination of Category-3 fertiliser with SRM, but the RA did not consider the scenario of an abattoir not implementing any SRM removals, as this was very unlikely due to the necessary processing sequence at abattoir. However, the RA did not consider the possibility of the importation of fertiliser or Category-3 materials. It is assumed in the RA that import risk equals any export risk that may occur.
39. The Chair concluded the discussion by saying the difference in absolute risk between the rendering methods was not the important question for Defra to consider, but it should rather be the risk of re-generating an increase in the BSE epidemic. The key issue was to consider the matter holistically and in particular how a effect of a relaxation in one Regulation might be altered by a possible relaxation of others. Although unlikely, relaxation here might allow another TSE to emerge and this should additionally be considered.

#### **ITEM 8 – FUTURE OPERATION OF SEAC (SEAC 103/4)**

40. The Chair reminded Members that he had recently written to them about proposals on the future operation of SEAC. The Chair asked Members of the Committee for their views on the suggestion that SEAC should henceforth aim to conduct the majority of its business in correspondence, only meeting when there was a major new development, or a significant amount of business over a short period.
41. Some Members were in favour of what was being proposed and suggested that business conducted by e-mail could usefully be confined to a scheduled period, or periods, in the year. It would be

important to retain the level of transparency that currently applies to the Committee's public Meetings. The Secretary noted that not only the conclusions reached but the initial discussion papers and summary of the e-mail discussion could be placed on the SEAC Website to ensure the present high level of public visibility was maintained. Members said that, by using the Website in this process, it might be possible to widen the public debate on the issues being discussed and draw on the scientific knowledge available around the World. Members agreed that the new process should be trialled, perhaps for a year, and then reviewed.

42. Other Members had doubts about this process and felt that Meetings were still needed. There were concerns that issues coming to the Committee in e-mails, particularly if they were not at scheduled times, would not be given the priority and the proper consideration that they deserved. The quality of discussion and cross fertilisation of ideas that can be achieved in face-to-face meetings would not be easy in e-mail correspondence. In particular, there was a view that Reserved Business Sessions could only be efficiently run in a face-to-face process. A further concern was that by not meeting on a regular basis the Committee might find itself marginalised when Departments required advice.
43. In answer to a question from a Member, the Secretary said that there was no proposal to change the procedures currently in place for making use of Sub-Committees.
44. The conclusion of the discussion, as summarised by the Chair, was that some regular Meetings of SEAC still needed to take place, but that some SEAC business could henceforth be carried out by e-mail correspondence, where appropriate, and subject to review. The email process would be structured, and limited to fixed times of the year and the process would be recorded on the SEAC Website so that the decision-making process was transparent and available for public scrutiny. The Secretary was asked to examine the pattern of SEAC business over the last few years and the number and timing of requests for advice from Departments in order to assess the number and timing of likely Meetings that should be arranged in the future. Additionally, the Secretariat should identify dates in 2010, and inform Members of these, so that they could place in their diaries and keep free to allow these Meetings to be organised easily.

## **ANY OTHER BUSINESS**

45. There was no other business. The Chair closed the Open Business Session, thanking all those who had presented information to the Committee and all who attended the meeting.