SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Minutes of the 104th Meeting held on 5th March 2010 at Royal Horticultural Halls and Conference Centre, Greycoat Street, Westminster, London SW1P 2QD.

Members: Professor C. Higgins (Chair)
Professor J. Collinge
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. M. Noterman (DH)
Ms. L. Redmond (FSA)

Technical Experts: Dr. P. Bennett (DH)
Mr. P. Burke (Defra)
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)
Professor S. Bird (MRC)
Dr. J Clewley (HPA)
Professor N. Gill (HPA)
ITEM 1 – INTRODUCTION

1. The Chair welcomed everyone to the 104th 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of Practice, there would be a short Reserved Business Session, after the Open Business Session, to discuss preliminary unpublished data.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 Chair offered sincere thanks to Deputy-Chair, Mr Peter Jinman who was attending his 43rd but last SEAC Meeting after the maximum ten years permitted service on the Committee. The Chair said that Mr Jinman had brought a wealth of veterinary experience to the deliberations of the Committee and a very practical and common sense approach to difficult issues. Other Members also expressed their gratitude. The Chair said he was happy to announce that Professor Graham Medley had agreed to take over the position of Deputy Chair.

3. 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.

4. 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.

5. The Secretary said the next scheduled Meeting of SEAC will be on 22 October 2010. However, the next meeting of Members of the Committee will be at a Joint Meeting of the UK TSE Committees, namely the Advisory Committee on Dangerous Pathogens TSE Working Group, the Advisory Committee on Decontamination Science & Technology, the Advisory Committee on the Safety of Blood Tissues and Organs, the CJD Incidents Panel & SEAC. This meeting will be held on 17 June.

6. Apologies for absence were received from Professors Jean Manson and Margaret Stanley.
ITEM 2 – APPROVAL OF MINUTES FROM SEAC 103 (SEAC 104/1)

7. The minutes of SEAC 103 were agreed as a correct record after one change, namely in paragraph 9, third sentence, where “that this change arose” should be replaced with “the frequency of the mutation increased”.

ITEM 3 – CURRENT ISSUES

8. The Chair said that prior to the Meeting, Members of SEAC had been sent three recently published papers on research on the requirement of axonal prion protein to maintain peripheral myelin, on diagnostic test accuracy for sporadic CJD against patients with other dementias and on characterisation of sporadic and variant CJD brain reference materials. Members agreed that there were no pressing issues emerging from these papers that required the Committee’s further consideration at this time.

ITEM 4 – vCJD PREVALENCE (SEAC 104/2)

9. Professor Noel Gill (Health Protection Agency) updated the Committee on progress with vCJD prevalence studies. Professor Gill said that the Health Protection Agency (HPA) has started collecting samples for a new study of 30,000 stored appendices, which will be tested by immunohistochemistry (IHC). The pilot study for a post mortem study of spleens will also begin shortly. The pilot will test a number of methodologies for obtaining consent for tissue samples to be removed, involving coroners, NHS bereavement services, and NHS Blood and Transplant. However, progress with engaging coroners has not been as good as hoped for. The HPA expect to be able to report on the outcome of the pilot in the next 3-4 months.

10. In respect of the National Anonymous Tonsil Archive (NATA), 85,000 pairs of tonsils have been tested by dual enzyme immuno assay (EIA), including 16,260 in the 1961-1985 birth cohort. No sample has tested positive. However, 10,000 were subject to

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testing by IHC, and a single follicle in one sample had tested positive, using two different primary antibodies. Extensive further testing of the tissue sample by IHC and Western Blotting was negative. It has also not proved possible to test another section from the same follicle. The HPA’s expert advisory group on large scale tissue testing was cautious about recommending transmission studies and recommended the further exhaustive IHC and Western Blotting (WB) testing, all of which was negative.

11. A Member asked whether the positive tonsil finding indicated a prevalence of 1:85,000 or 1:10,000. Professor Gill suggested 1:10,000. A Member asked about the sampling structure for the 10,000 samples by IHC, and the pre-set criteria for determining positive results. Professor Gill responded that the 10,000 samples were from the 1961-85 cohort, with the addition of a few hundred extra samples that had high negative readings on dual EIA. The positive sample was from the 1961-85 cohort, but would not have been designated a positive by the preset criteria for the study because those criteria had been developed for the dual EIA testing system.

12. A Member noted that the genotype of the positive samples in the Hilton study had been unexpected, and asked whether the new appendix study would be segmented by genotype. Professor Gill responded that prior genotyping of all specimens would not be used as a means of selecting a sub-set of appendices for IHC testing, but that any IHC positive specimen that was found would be genotyped.

13. A Member suggested that the positive tissue on the slides could be used for transmission studies; however, another Member thought that it was highly unlikely to succeed since it had been tried previously with the positive samples from the Hilton study. A Member noted that IHC is the most sensitive test available, and it is possible to find samples that are positive by IHC but negative by Western Blotting. This is supported by evidence from diagnostic tonsil biopsies, which in some cases found just a few follicles to be positive.

14. The Chair felt it was unlikely that much more could be done to confirm whether the result was a true or a false positive. Instead, the question that needed to be addressed was how this single positive result, assuming it is indeed positive, would affect the

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estimation of prevalence. The Committee agreed that even though the positive sample suggested a possible prevalence of 1:10,000, the result from the Hilton data of 1:4,000 would still remain the most precautionary figure for risk management purposes.

15. Dr Peter Bennett (DH) argued that it is necessary to be precise about what is meant by prevalence. The DH surgical instrument risk assessment assumes a single concept of prevalence, with all lymphoid tissues being infective all of the time. However, the situation could refer to a number of scenarios, such as the prevalence of vCJD infections in the population as a whole, the proportion of people who have abnormal prion protein in specific tissues of their bodies at specific times or the number of people who have vCJD infectivity in some or all of their tissues.

16. Dr Bennett said the new appendix study would start with IHC testing of stored appendices. If no positives are found after 30,000 samples have been tested, the study will stop and SEAC’s views will be sought. If positive samples are discovered, the plan is to attempt to switch to fresh samples which would be subject to other forms of testing, enabling comparison with positive samples found by IHC. It should be noted, however, that the organisational challenge of assembling the very large number of fresh appendix specimens likely to be required would be greater than that of collecting fresh tonsil specimens – largely due to the organisational differences between acute surgical appendicectomies and elective tonsillectomies.

17. A Member noted that the issue of timing had not been addressed. The NATA tonsils are being collected 10 years after the Hilton appendices, but prevalence will not have remained the same in the same age groups over that time. What is needed are data over a period of time, which will indicate whether prevalence is increasing or decreasing. The proposed post mortem archive offers the opportunity to achieve that. A Member also highlighted that there is a number of potential cohorts of interest, such as blood donors. The Chair stated that the NATA data will not influence the estimate of prevalence because the accumulation of PrP in tonsils may be different from the accumulation of PrP in other tissues, and there may also be genotype effects at work. The Chair suggested that even if this finding of a positive sample in the NATA study is a true positive, it would not negate the Hilton data.

18. The Chair said the main questions to answer for public health purposes were: how many individuals are infected with vCJD; and what proportion of them will develop clinical disease and/or be
capable of transmitting infection to others? He suggested that there is a need to focus on the worst case, which is currently represented by the Hilton data. The Chair stated that the post mortem study could have sufficient power to provide an answer to these two main questions.

19. A Member asked if there were means of compelling coroners to take part in the study. Dr Bennett responded that DH is waiting for the evaluation of the pilot study before deciding how to proceed.

20. A Member suggested that the focus should not exclusively be on the worst case, and other Members suggested that whilst the NATA data might not reduce the worst case estimate, these would nevertheless allow for a more likely estimate to be determined for central planning purposes. Another Member suggested that it might be possible to establish a model-based central estimate that does not take one study over another but considers a range, that also takes cohort effects into account, and was consistent with case numbers.

21. However, another Member stated that there are biological reasons that could account for lower levels of PrP in tonsils than in appendices, and that the falling number of clinical cases of vCJD does not say anything about the prevalence of sub-clinical infections (or “carriers”). It is not known what proportion of those infected will ever have infectivity in their lymphoreticular system, because the lymphoreticular systems of clinical vCJD cases may be distinctive (and part of the reason for their susceptibility to clinical vCJD following BSE prion exposure). The prevalence studies might give early warning of a significant development, but even a zero positive result would not provide much reassurance since the test sensitivity to detect carriers is unknown.

22. There was discussion about whether the NATA study should be continued to its planned end of 100,000 samples. Professor Sheila Bird (MRC) suggested that there is a case for IHC testing of samples from those born since the 1990s. If there are no positives in that age cohort, but positives continue to accumulate in the indicative age groups, that would be instructive. Dr Bennett suggested that if the figure of 1:10,000 by IHC testing of the 1961-1985 cohort samples is considered to override the 0:16,000 by EIA testing, there is no point EIA testing another 4,000 samples from that cohort.

23. There was some discussion of whether to divert IHC capacity to other age cohorts in the NATA study. Professor Bird suggested
focusing NATA on the younger age group and the appendix study on older age groups. Both would have sufficient power to influence current estimates of prevalence.

24. A Member suggested that there is a helpful dialogue to be had with the risk management committees, in order to ascertain what risks they need assessed, e.g. risks in paediatric surgery or risks from blood.

25. The Committee agreed that:

- It is difficult to ascertain the sub-clinical prevalence of vCJD through surrogate studies of the presence of abnormal prion in different tissues.
- It is not known whether different tissues accumulate prion protein to different extents in sub-clinical infection, and thus any prevalence can only be assumed to be for the tissue examined and not necessarily for the population as a whole.
- The Hilton data should be used as the worst case data for prevalence, unless these are proved incorrect by further study.
- The design of the new appendix survey should have sufficient power to enable it to be used to assess Hilton data accuracy.
- The proposed post mortem study could have sufficient power to influence estimates of prevalence, if an appropriate number of coroners participate.
- NATA should continue up to the planned 100,000 samples but any continuation beyond this is unlikely to provide further useful information.

ITEM 5 – vCJD TRANSMISSION VIA BLOOD COMPONENTS (SEAC 104/3)

26. Professor Sheila Bird joined the Committee for discussion of this item. Dr Peter Bennett (DH) presented a paper which sought advice on how to establish a plausible range of scenarios for blood borne transmission of vCJD, for risk management purposes. The scenarios which DH currently use for risk management employ combinations of “high” and “low” values for three key inputs namely the sub-clinical prevalence of vCJD, the infectivity in blood components and the susceptibility of blood recipients to clinical disease. However, a number of these scenarios over-predict the number of clinical cases of vCJD that are known to have resulted so far from blood-borne transmission. DH needs advice on establishing a range of scenarios which are more consistent with
the available “positive” and “negative” evidence on human transmission, as well as with the findings of animal studies.

27. Dr Bennett said that there may be some additional factors concerning susceptibility beyond what is known about genotype, or else the prevalence of infective donors is not as bad as suggested by the available evidence. A Member suggested that a combination of susceptibility and infectivity could be the critical factor.

28. The Chair noted that the available data suggest that the worst case estimates do not seem to be as bad as originally anticipated, but that the problem lays in ascertaining how much better than the worst case the situation actually is.

29. A Member suggested that multiplication of averages might not be justified in these estimations as donation behaviour is highly skewed with many individuals donating frequently. However, it could be that there is nothing wrong with the assumptions being made, but simply fortunate that donors have not been infected.

30. A Member reported the use of a model simpler than used by DH and this had led to slightly different results. Millions of different scenarios had been run, but only those consistent with the observed number of cases were considered further. The model allowed for multiple genotypes, as well as lower susceptibility assumptions and longer incubation periods. Central estimates had been considered for each parameter and some uncertainties ignored. That work had indicated that blood transfusion may not be an efficient route of transmission. It is possible to generate secondary epidemics similar to the size of the primary epidemic, but it would probably not be possible to link all cases back to blood borne transmission.

31. The Chair asked the Committee if any major factors had been missed. A Member suggested that the incubation period of the disease as well as genetic effects might account for why there had not been more blood borne cases. The DH paper assumes that the incubation period of primary transmission is 10-12 years, but there have been no cases with onsets below 13 years for vCJD. In the case of kuru, the range of incubation period is extremely broad, from 5-56 years. For vCJD, one possibility is that many people are infected but it may be many years before it becomes apparent. A Member suggested that there were wider biological parameters in genetics and immunology which will impact on the question of
32. A Member stated that no allowance has been made for the age distribution of donors in the assumptions on prevalence. The “low” scenario of 1:20,000 is actually closer to being a central estimate, with the Hilton data being applicable to the highly exposed cohort. The small number of cases of blood borne transmission of vCJD is consistent with the low scenario, but the lack of data, especially from the highly transfused, and lack of post mortem data from the six patients who received vCJD implicated blood but died of unrelated causes, means that the full picture is not available yet regarding the highly transfused. However it is irretrievably missing regarding the six recipients who died without vCJD-informative testing having been done post-mortem.

33. A Member noted that tissue samples used in the prevalence studies are taken from people who are ill with an intercurrent infection, whereas blood is donated by healthy volunteers, and asked whether there is any evidence that prion accumulates in tissues because of the intercurrent infection. Another Member responded that there is evidence that chronic inflammation can act as a focus for prion propagation and so such an hypothesis is not completely implausible.

34. The Committee agreed with the proposition that the scenarios need to be calibrated to the observed data. The Committee concluded that nothing had been missed in the DH paper, although some of the assumptions used could be refined and when this was done there may not be a statistical discrepancy between the predicted and observed number of cases. The Chair recommended an on-going dialogue between DH and Members of the Committee in order to further refine the analysis in the paper.

ITEM 6 – MODELLING OF BSE SURVEILLANCE STRATEGIES IN CATTLE (SEAC 104/4)

35. Dr Amie Adkin (VLA) presented an overview of BSE surveillance modelling strategies that investigated the impact of different BSE testing scenarios and the efficiency of surveillance. Three different approaches were used to assess efficiency of surveillance. The first two methods were based on the VLA’s BSE control model which had previously been assessed by SEAC. The first looked at the number of test positive cases that may be missed by raising the age at which cattle were tested and the second method investigated the time taken for re-emergence of disease to be
detected. The third approach assessed the efficiency of different surveillance strategies using a modified version of the BSurvE model\(^5\). Four BSE cattle testing scenarios were examined using each approach, reflecting the testing regime in place prior to January 2009, the current regime of testing Healthy Slaughter (HS), Emergency Slaughter (ES) and Fallen Stock (FS) older than 48 months and two hypothetical scenarios in which HS, ES and FS were tested at more than 60 months and more than 72 months.

36. Dr Adkin explained that the mean number of test positive cases missed for all cattle streams over the three year period 2009-2011 was 0.17 for 48 month testing, 0.84 for 60 months and 2.01 for 72 months. These results assume a constant prevalence has existed since the last observable cohort. To investigate the time taken for a re-emergence of disease to be detected, the model used a rate of re-emergence of 40\%, this being based on the rate observed during the 1984-1989 BSE epidemic and considered a worst case scenario in the light of current controls on intra-species recycling. The threshold at which a new epidemic would be identified was defined to be when the estimated mean number of cases under increasing prevalence breached the 95\(^{th}\) percentile observed under a constant prevalence. The model showed that for all active and passive surveillance a re-emerging epidemic would be observed in all BSE cattle testing age scenarios apart from HS animals greater than 72 months. However, Professor Bird believed that the re-emergence rate was not clearly defined in the model description and, noting that the limited time-frame on which model outputs were concentrated, even if testing were limited to 72 months or more, a re-emergent epidemic must be able to be identified.

37. Finally, Dr Adkin described the BSurvE model which allowed a quantification of the overall effectiveness of BSE surveillance. The model determined the ratio of the exit probability of a detected, infected animal, to the exit probability of an uninfected animal. The results showed that overall there was a negligible impact from HS on the effectiveness of surveillance and a small impact from ES and FS for all four testing age scenarios. Clinical suspects (CS) had the greatest impact with those animals over 84 months contributing the most.

\(^5\) BSurvE is a model developed by Massey University’s EpiCentre and was initiated as a project conducted by the European Union TSE Community Reference Laboratory and the VLA. The model is used to estimate BSE infection in national herds, evaluate national surveillance programmes and provides a tools for optimising surveillance activities for infected and uninfected countries. [http://www.bsurve.com/](http://www.bsurve.com/)
38. Opening the discussion a Member noted that there was a number of uncertainties that needed to be acknowledged when interpreting the output of these models. Some of the parameters in the models were based on assessor assumptions and it was important to determine how accurate these assumptions were and their significance on any result. There was concern that when using data from one model to inform a second, if any assumptions had changed and had not been re-examined it would have implications for any outputs of the model. The Member also highlighted that the model assumed that there was no illegal activity or incorrect movement of animals. This would be unlikely to prevail in the instance of a newly emerging epidemic. The model should be refined to take account of actual practice.

39. Dr Adkin responded that in the sensitivity analysis none of the parameters based on assessors’ assumptions were identified as significantly influencing the outputs. The assumptions highlighted by the Member impacted on the accuracy of the model’s estimates of infectivity entering the food chain, rather than its ability to model the number of missed BSE cases, the latter being the issue under consideration. Regarding illegal activity and cattle movements, the British Cattle Movement Service and VLA test data were compared and used to populate this parameter. Further, the number of animals identified by the FSA as missing testing (average of 4 per year in GB since 2006) was insignificant given the total number of cattle tested per year (average of 400000 per year in GB since 2006).

40. A Member added that there was an assumption in the model that a re-emergence would be observed in the same adult population as the initial BSE epidemic. This had to be examined further to determine whether this was a reasonable assumption. Further, a Member added that if this was the case then under the current testing it would result in a long period of time before CS cattle were identified as a problem if it appeared at a younger age or even longer if the age of compulsory testing was raised further. As a result, there would be a number of animals in the system before the alarm was raised. The model also did not consider whether any re-emergence would be picked up if it appeared in a young age cohort. The assumption that a definite clinical case would be observed within a month of starting to display clinical symptoms was also considered optimistic. Mr Patrick Burke (Defra) said that the veterinary surveillance strategy had been in place since 2004 and was developed from learning the lessons from the BSE crisis. The strategy includes the RADAR system and scanning surveillance network is in addition to specific BSE surveillance.
Defra considered that, if there was an emerging disease, the coordination and detection of disease would be better than it was during the first BSE epidemic.

41. A Member added that SEAC had informed the FSA that it was content with the previous BSE control model assessment as long as surveillance was maintained at the highest level. Therefore, it was important to identify the sensitive points which impact on the results of this study. It was added that SEAC needs to be confident that CS animals were measured and considered in the model as resurgence of BSE might be first seen in this category of animal. It was also questioned whether it would be better to test ES cattle at a younger age than HS. This is not currently done, particularly if people do not adhere to the rules governing the declaration of ES with the current testing age. Dr Adkins responded that as the age limits for the testing of animals had changed so had the reporting definitions (i.e. previously cattle could only be considered HS up to thirty months, however new legislation means HS includes cattle up to 48 months) leading to different populations in the datasets which may cause difficulty in obtaining the correct age matched data to perform the work.

42. A Member added that two important questions were being asked: firstly, how many animals are missed by surveillance; and secondly, can re-emergence be recognised. It was felt that the assumptions used in determining re-emergence contradicted the outcome of the model. The model assumed that the re-emergence scenario starts in the 2002 birth cohort and continues to propagate that way; if this were the case Members could not see how the figures for BSE-infected cattle in subsequent years, as determined from the model, were arrived at. Dr Adkin stated that, due to the model assumptions, it takes a number of years for the disease to reach significant levels of prevalence in the population in order that cases would be identified. There appeared to be confusion around the use of prevalence in the model; rather than prevalence, surely it is incidence that should have been used when calculating a re-emerging epidemic. It was also considered incorrect to compare the 95th percentile of distributions for the emergence of infectious diseases. Other methods were considered more sensitive and could potentially lead to the observation of the age cohort effect.

43. Professor Sheila Bird added that if one had an emergent infection with more infections each additional year, then within two to three years BSE cases would be observed in FS. It was considered that in an emergent infection one would typically find the first BSE cases in the young adult animals. Professor Bird added that with
the change to 48 month testing for FS and ES, the potential for noncompliance was vast. It would have benefited the Committee if empirical data had been shown on the age distribution of tested animals in the FS and ES prior to, and after the change. This would identify any impact on the submission of animals for slaughter just prior to the 48 month limit to avoid inspection. In response to the age at which BSE cases would be first identified Mr Burke commented that the first recorded clinical cases recorded in the mid 1980s were in mature cattle, not the young cohort.

44. In answer to a question from a Member about the frequency per age-at-slaughter in months, per exit stream, around revised test thresholds, Dr Adkin responded that the increase in the age of testing for HS from 30 months to 48 months in January 2009 had relatively little impact on the numbers of cattle slaughtered aged under 48 months and over 48 months respectively, because the majority of HS cattle were prime beef animals aged less than 30 months. However, a Member added that the problem was not with the HS but with the ES and FS. It was important to recognise that due to changes in the testing age of cattle there would be a change in the type of animal in the ES and FS streams, for example, beef cattle would continue to go into the HS stream due to their younger age whereas the older cohorts would be populated with milking herds. One would also be moving into an aged population where those with disease had already been removed resulting in a very different type of subset.

45. In summing up the Chair noted that the Committee had significant concerns regarding the way in which these models might be used. It remained important that SEAC was assured that surveillance was in place, as other controls are relaxed, to quickly detect any increase in prevalence and/or possible re-emergence of disease. If surveillance was to be effective it had to be appropriate to ensure the time taken between the event which caused a re-emergence, and the ability of surveillance to detect it did not pose a significantly enhanced risk to the consumer.

46. In general the Committee felt that the re-emergence model was not providing a clear output and Members were unable currently to conclude that there would be little change to the human health risks derived from potential changes to surveillance. It was agreed that Dr Adkin would continue the discussion outside of the meeting with Professor Bird and expert Members of the Committee to consider the assumptions used in the model and to clear up any remaining queries.
ANY OTHER BUSINESS

47. 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.