



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Draft minutes of the 99th meeting held on 14th December 2007

Novotel Hotel, Schooner Way,
Cardiff CF10 4RT

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

Assessors: Ms. S. Eades (Defra)
Dr. A. Gleadle (FSA)
Dr. S. Hayes (NAW)
Mr. M. Noterman (DH)
Dr. A. Douglas (AFBINI)

Technical Experts: Dr. P. Bennett (DH)
Mr. P. Burke (Defra)
Professor N. Gill (HPA)
Dr. D. Matthews (VLA)

Acting Secretary: Dr. T. Barlow

Secretariat: Mr. B. Cole
Dr. D. Cutts
Dr. A. Patey
Dr. C. Ravirajan

Also in attendance Mr Barry Cockcroft (DH) for item 11
Dr. J. Clewley (HPA) for item 10

Mr. P. Comer (DNV Consulting) for item 6
Mr. A. Gresham (Defra) for item 5
Dr. P. Grove (DH) for item 11
Dr. J. Hope (VLA) for item 7
Mr. S. Reaney (VLA) for item 6

DRAFT

ITEM 1 – CHAIR’S INTRODUCTION

1. The SEAC Chair welcomed everyone to the 99th meeting of SEAC, the second in Cardiff. He thanked the National Assembly of Wales for hosting the meeting and a dinner for SEAC members the preceding evening, and Ms Carol Pring and Ms Natalie Price for working with the secretariat to help organise the meeting.
2. The Chair explained that Dr Peter Grimley had been appointed as SEAC Secretary and would take up the post from 14th January 2008. He thanked Dr Tom Barlow (Acting Secretary) and the secretariat for their truly excellent work in organising the meeting in the absence of a Secretary.
3. The Acting Secretary explained that open meetings allow the public an opportunity to observe the committee at work and provide 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. Short summaries of the discussions would be published on the SEAC website.
4. Apologies for absence had been received from Professors John Collinge, Corinne Lasmezas and Alun Williams and Mr John Bassett. The next SEAC meeting is scheduled for Friday 15th February 2008 and will take place at Royal Horticultural Halls and Conference Centre, Westminster, London.
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 98 (SEAC 99/1)

6. The minutes of open and reserved business sessions of SEAC 98 were agreed as a correct record.

ITEM 3 – CURRENT ISSUES

7. SEAC discussed the following issues:

- Given the evolving nature of scientific understanding of TSEs, it is suggested that a procedure be instigated for the use of SEAC advice by Government Departments. Members agreed that Government Departments should state the date when SEAC opinions were given when referring to opinions. In addition, SEAC and departmental officials agreed that it would be important for departments to consider whether new information had emerged that could alter a SEAC opinion and to refer these data to the secretariat to allow the SEAC opinion to be reviewed prior to its use by a department.
- A member explained that a confirmed case of atypical scrapie had been recently identified in a research project at the Institute of Animal Health (IAH). The animal had been born in 1997 in New Zealand, imported into the UK in 1998, spending the first six months at the Arthur Rickwood Sheep Unit (ARSU) before transfer to the IAH site at Compton. Thus, it is possible it may have become infected either in New Zealand, whilst at ARSU, where two other cases have now been confirmed, or at Compton, perhaps as a result of the experiments conducted during the research study involving transfusion of blood between sheep. The case is under further investigation.
- Members considered a report describing a case of Creutzfeldt-Jakob Disease (CJD) of prion protein gene codon 129 VV genotype who had died in 2000 at the age of 39 years old. The case had unusual neuropathological features and abnormal prion protein (PrP^{Sc}) western blot banding pattern¹. One possible interpretation of these data was that this could represent the first case of vCJD in an individual of VV genotype. However, members noted that the clinical, cerebral Magnetic Resonance Imaging and neuropathological features were within the range previously observed with sporadic CJD (sCJD). Although there were similarities between the molecular features of PrP^{Sc} in the case and those of cases of vCJD, they were not identical and only strain typing mouse bioassays could provide conclusive evidence about the causative transmissible spongiform encephalopathy (TSE) agent. The paper stated that transmission studies of this case, in transgenic mice, were being undertaken but there was no information about the current status of these experiments. The Chair asked the Acting Secretary to contact

¹ Mead *et al.* (2007) Creutzfeldt-Jakob disease, prion protein gene codon 129VV, and a novel PrP^{Sc} type in a young British women. *Arch. Neurol.* 64, 1780-1784.

the research group to ask about such transmission experiments.

- A member informed SEAC that the Department for Environment, Food and Rural Affairs (Defra) was consulting on cost and responsibility sharing for animal health and welfare² and that this included specific proposals for TSE controls between government and industry.

ITEM 4 – REPORT FROM THE SEAC SHEEP SUBGROUP (SEAC 99/2)

8. As the SEAC Chair had been the Chair, and the Deputy Chair a member, of the SEAC Sheep Subgroup, Professor Stanley agreed to chair the discussion of this item.
9. Professor Higgins introduced the SEAC Sheep Subgroup report, explaining that the Subgroup had considered four issues (i) the origins of two cases of atypical scrapie in the ARSU sheep flock established and managed to minimise the risk of infection by TSEs and the implications for research using animals from the flock, (ii) the interpretation of findings from experiments to characterise the strain of infection in two historic sheep TSE cases and the implications for current understanding of the possible presence of bovine spongiform encephalopathy (BSE) in sheep, (iii) the implications of early data from a study of bottle feeding milk from classical scrapie infected ewes to TSE-free lambs, and (iv) the implications of cases of classical scrapie in ARR/ARR sheep for the scientific basis of the National Scrapie Plan (NSP). He summarised the key conclusions in report on each issue.
10. In relation to (i), members agreed that the report should be updated to reflect the identification of a third confirmed case of atypical scrapie associated with ARSU (as discussed earlier), noting that the case had been resident at the Unit for only six months.
11. Dr Danny Matthews (Veterinary Laboratories Agency [VLA]) noted that all three of the atypical scrapie cases associated with ARSU are of the Cheviot breed and two were homozygous and one was heterozygous for the AFRQ allele. It was possible that the sheep carrying this allele may be susceptible to atypical scrapie that arises spontaneously.

² Defra consultation on sharing costs and responsibility: animal health and welfare. <http://www.defra.gov.uk/news/latest/2007/animal-1211.htm>

12. Members asked what measures might be taken to minimise the spread of atypical scrapie at the site referred to in paragraph 15 of the report and were informed that manure from the Unit had been spread on adjacent farmland, which provided a source of straw of the Unit. It had been suggested this practice might represent a potential route for recycling of the atypical scrapie agent, and may be inadvisable.
13. In relation to (ii), members noted there were four hypotheses for the interpretation of the findings from passage of two sheep TSE cases in mice: an experimental error had occurred, the features observed may be a normal consequence of passage of classical scrapie isolates in the breed and genotype of sheep, a strain conversion may have occurred or the features observed may reflect a mixed BSE-classical scrapie infection in sheep.
14. Dr Matthews explained that an internal audit had found no evidence of experimental error but an independent audit was planned with Professor Alun Williams as the scientific advisor. Dr Jim Hope (VLA) explained that the suggestion that the features observed on strain typing of two sheep TSE cases may be a normal consequence of passage of classical scrapie isolates from the particular breed and genotype of sheep, had arisen as one of the cases was an ARQ/ARQ Swaledale. Sheep of this genotype and breed rarely succumb to classical scrapie. Only one other case of classical scrapie in an animal of this genotype and breed had been strain typed by mouse bioassay with the features on passage consistent with classical scrapie.
15. The Chair considered that of the four possibilities, the first two appear to be the least likely, the third possibility may be the most likely but is unproven and the fourth possibility cannot be excluded. It is important to note that the features observed on mouse bioassay are not consistent with features observed when BSE is passaged in mice. If the findings did reflect a mixed BSE-classical scrapie infection, the isolates were from historic sheep TSE cases and the probability of mixed infections was low. Thus, there is no indication from these data of a current significant risk to human health from BSE in sheep.
16. A member asked why the report only considered mixed infections of classical scrapie and BSE rather than atypical scrapie as it is known that classical and atypical scrapie can occur together. The Chair explained that as the report described the analysis of two sheep TSE cases that discriminatory testing indicated were cases

of classical scrapie, only mixed infections of classical scrapie and BSE had been considered.

17. A member suggested that less certainty should be reflected in the estimate of the probability of mixed infection arising (footnote 8 of the draft report) as the estimates relied on an assumption that BSE and classical scrapie would occur independently. In addition, it was incorrect to state that the most likely prevalence of BSE in sheep was zero (paragraphs 32 and 39 of the draft report); the sample gives an estimate of the maximum prevalence that is consistent with the results of the survey.
18. In relation to (iii), Dr Matthews indicated that additional data from the study obtained after the Subgroup meeting supports the conclusions that milk may be an effective route of transmission of classical scrapie. These data have been included in a paper accepted for publication. Members noted that the somatic cell counts had been high in milk given to the lambs and thus clinical mastitis may be a confounding factor in relation to the transmissions observed. Dr Matthews noted that there was evidence from published literature that high somatic cell counts can occur in the absence of mastitis. Furthermore, further examinations at the VLA had failed to identify evidence for the presence of mastitis in the study sheep.
19. Members had no comments in relation to (iv).
20. SEAC endorsed the report subject to minor amendments to reflect the discussions above.

ITEM 5 – SCIENTIFIC BASIS OF CLASSICAL SCRAPIE CONTROLS (SEAC 99/3)

21. Mr Andrew Gresham (Defra) gave an overview of the background and policy context of the issue. The European Court of First Instance had, following an application by the French Government and, pending a full hearing, suspended clauses in new European Commission legislation to allow sheep from classical scrapie affected flocks to enter the human food chain if testing negative for TSE. The UK intended to support the Commission at the full hearing but wished to seek SEAC's advice in relation to possible links between classical scrapie and human TSEs and the performance characteristics of discriminatory tests for sheep TSEs. SEAC had been provided with the opinions of the French Food Safety Authority (AFSSA), the European Food Safety Authority (EFSA) and the German TSE advisory committee (KOM AG TSE)

that had considered these issues. Advice from SEAC could be incorporated into a UK submission to the Court.

22. A member noted that the AFSSA opinion reflected concerns that as a consequence of the release of animals from classical scrapie-affected sheep flocks into the human chain, cases of undiagnosed BSE may also be inadvertently released into the food chain. Furthermore, a greater number of classical scrapie infected sheep may enter the food chain even though it is not possible to exclude a risk to human health from classical scrapie. Three key uncertainties had been identified by AFSSA, EFSA and KOM AG TSE, although there were some differences in emphasis about the uncertainties in the opinions. The uncertainties related to (i) the capability of tests to detect TSEs in sheep during the stage when PrP^{Sc} is accumulating in the periphery only, (ii) the ability of the tests to detect BSE when another TSE is present and (iii) the evidence suggesting a lack of link between human and animal TSEs other than BSE. In relation to (iii), observations that classical scrapie has been an endemic disease in sheep for more than 200 years without any apparent association with human disease, and that sporadic Creutzfeldt-Jakob Disease (sCJD) exists in countries such as Australia and New Zealand with no reported cases of classical scrapie, are incontrovertible. However, it should be noted that it would be very difficult to demonstrate an epidemiological link between such relatively rare diseases in animals and humans. Authors of two epidemiological studies^{3,4} that had examined risk factors for sporadic Creutzfeldt-Jakob Disease (sCJD) dismissed a link between classical scrapie and sCJD. However, these data could be interpreted differently to suggest a potential link, this could be a chance association arising from biases inherent in the design of these retrospective studies. It was therefore important not to be completely dismissive of a lack of a link as it would be very difficult to prove an epidemiological link between such rare diseases.
23. Members noted that, although there is no evidence for a risk to human health from classical scrapie, a risk could never be ruled out. However, even if there is a risk, the risk must be very small indeed as the observed prevalence of sCJD is very low.
24. Members considered that it was not possible to quantify any increase in risk from classical scrapie that would arise from

³ van Duijn *et al.* (1998) Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. *Lancet*. 351, 1081-1085.

⁴ Brown *et al.* (1987) The epidemiology of Creutzfeldt-Jakob disease. Conclusion of a 15-year investigation in France and review of the world literature. *Neurology*. 37, 895.

changing the classical scrapie controls as set out in the new regulations. However, it is unlikely that the risk would be greater it was before controls for classical scrapie were introduced. Indeed, given the effect of the NSP in reducing the incidence of classical scrapie, the risk was likely to be less than prior to the implementation of classical scrapie controls.

25. A member noted that the health implications of atypical scrapie are not yet understood. Since atypical and classical scrapie can occur in the same flocks, changes to the controls for classical scrapie may result in an increase in the number of atypical scrapie infected animals entering the food chain. The changes to the control measures relate to classical scrapie and even if they increased the amount of atypical scrapie infectivity entering the food chain that increase would be very small. There is increasing epidemiological evidence to suggest that atypical scrapie might have existed for considerable time: it is widely distributed in Europe despite, as the lack of confirmed clusters of cases suggest, being relatively non-infectious. Therefore, atypical scrapie, like classical scrapie, may be a disease of low to negligible human health risk. However, its emergence as a new disease that may be a risk to human health cannot be completely ruled out.
26. Dr Matthews suggested that a key concern for the French authorities in relation to the changes to the controls may be around the lowered detection rate of younger animals incubating classical scrapie peripherally. Given their concern about a possible link between classical scrapie and human TSEs, the French had therefore decided to oppose a measure which might increase the level of classical scrapie infectivity entering the food chain from known affected flocks. UK surveys of culled animals from classical scrapie affected flocks indicated relatively low levels of infection in flocks, however in France classical scrapie appeared to be widespread in some culled flocks.
27. A member noted that culling of whole flocks on the identification of classical scrapie may adversely affect the willingness of farmers to report classical scrapie. This may increase the number of classical scrapie infected animals entering the food chain. Dr Matthews noted that the reporting of classical scrapie cases had dropped substantially in recent years. This may be a consequence of the NSP in reducing the incidence of infection but could be a consequence of a failure to report cases. Mr Gresham noted that the detection rate of classical scrapie cases in the abattoir survey had fallen which suggested a real fall in the incidence of classical scrapie due to the NSP. Members noted that reductions in the

prevalence of classical scrapie would reduce the potential human health risks of classical scrapie.

28. Members agreed that changes in the regulations would not significantly increase the risks to human health. However, a risk: benefit analysis would be required to fully understand the proportionality of the changes to the classical scrapie control measures. This was outside of SEAC's remit.

ITEM 6 – CONSIDERATION OF VARIOUS OPTIONS RELATING TO RELAXATION OF THE TOTAL FEED BAN (SEAC 99/4)

29. Mr Patrick Burke (Defra) introduced the policy context of the issue. He explained that in 2001, the EU extended the ban on feeding mammalian meat and bone meal (MBM) to ruminants to a ban on feeding animal protein to ruminants and processed animal protein (PAP) to all animals farmed for food production. At SEAC 89 (September 2005), Defra and the FSA sought advice from SEAC on the issues outlined in the EU TSE Roadmap which sought to ensure that any relaxation of the BSE controls, such as specified risk material controls, TSE surveillance and feed controls, as a result of the decline in the BSE epidemic, would be science-based and would not endanger either public health or the policy of eradicating BSE. In January 2007, the TSE Regulation was amended to provide a legal basis for the future options of feeding fishmeal to young ruminants and the introduction of a risk-based tolerance level for the presence of amounts of animal protein in feed caused through adventitious and technically unavoidable contamination. At SEAC 98 (July 2007) the committee considered it important that Defra should seek SEAC's view should a policy of feeding non-ruminant MBM to non-ruminants be proposed as part of the TSE Roadmap. Advice was now being sought from SEAC on the potential for new TSE infections and epidemics to arise if present feed controls were relaxed to allow the introduction of tolerance levels for certain types of PAP in feed, the inclusion of fish meal in young ruminant diets and the feeding of non-ruminant PAP to non-ruminants of a different species.
30. Mr Philip Comer (DNV Consulting) presented an overview of an assessment of the potential increase in exposure to BSE that could result in the European Union from allowing non-ruminant PAP to be used in feed for non-ruminant farm animals. The risk assessment is based on the EFSA risk assessment model⁵ and

⁵ The EFSA Journal (2005) Opinion of the Scientific Panel on biological hazards (BIOHAZ) on the "Quantitative risk assessment of the animal BSE risk posed by meat and bone meal with

uses the same assumptions where appropriate, for example for infectivity and contamination. The assessment estimated that on the basis of a 0.1% contamination of cattle feed with animal protein and a uniform distribution for contamination of the non-ruminant PAP with bovine MBM, the mean exposure was 0.0008 cattle oral infectious doses per year, an extremely small potential exposure. The controls in place for animal feed production would ensure that if such contamination was to occur it would be a rare event; thus this exposure represents a pessimistic scenario. He concluded that if PAP were to be used as an ingredient in non-ruminant animal feed it would not result in any significant level of exposure of cattle to BSE.

31. Mr Scott Reaney (VLA) outlined the performance of two analytical test methods in use for the detection of processed animal proteins in animal feedstuffs. The statutory microscopic method was considered a good screening tool with low sensitivity (< 0.1%) but was operator dependent, did not detect soluble proteins or soft tissue and had limited quantification and speciation capability. The newer real-time polymerase chain reaction procedure was species specific, had good limit of detection (< 0.2% MBM within a feed matrix) but gave no quantification and was not EU approved. Work to develop further methods was summarised.
32. Members noted that relaxation of control measures involved re-evaluation of the risks based on the current circumstances. In relation to BSE it is clear that the circumstances in recent years had changed considerably compared with the situation when the total feed ban was introduced as the risks from BSE had greatly diminished. Quantitative risk assessments should underpin the relaxation of control measures. However, risk assessments were dependent on assumptions made about the effectiveness of the regulatory position at the time. To obtain a reasonably accurate view on the risks when multiple changes to controls measures are considered, assessments should not estimate the effects of single changes in isolation but estimate the combined effects of numerous changes to controls as there may be interactions between various changes. However, it also has to be recognised that many of the risks are unpredictable and unquantifiable. This applies particularly to basing controls on estimated assay sensitivities and specificities (e.g. the accuracy of an assay for the species origin of PAP). The desired characteristics of a test depend on the context in which it is going to be used (e.g. the proportion of samples that are expected to be contaminated), and

respect to the residual BSE risk" 257, 1-30. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620776574.htm

the regulation regime in which it will operate (e.g. removal of batch versus legal prosecution).

33. Members considered that intra-species recycling of animal components via feeds for ruminant species should be avoided as it is known that this may give rise to TSE outbreaks, although there is no evidence of TSEs occurring in fish, poultry or pigs. Proposals to include PAP in feed for non-ruminants could potentially give rise to cross-contamination of ruminant and non-ruminant feed during feed production and storage. This could lead to feed including PAP from one species being fed to animals of the same species or to ruminants. This provides a potential route for BSE to be transmitted to cattle. Preventing such cross-contamination could be difficult to enforce therefore, elimination of BSE could not be assured in such circumstances. Mr Burke noted that the PAP would be processed from material formerly considered fit for human consumption, which would reduce the risks considerably.
34. Members noted that the risks from inclusion of PAP in animal feed depend on the extent to which the source of PAP and its inclusion rate can be controlled. Introduction of tolerance levels for adventitious and technically unavoidable contamination of certain types of PAP in feed depended on the availability of robust analytical methods and sampling procedures that would be capable of identifying the species and concentration of PAP to allow tolerance levels to be enforced. There are insufficient data on the performance of tests to detect and quantify PAP in feed under the situations they would need to be used to enforce regulations.
35. In relation to including fish meal in young ruminant diets, members considered that routes of contamination of fish meal with mammalian PAP could be envisaged, however because of the low prevalence of BSE, the risks were likely to be low and would not generate an epidemic. Nevertheless, members expressed surprise that this proposal relates specifically to young ruminants when young animals are considered to be the most susceptible to TSE infections. Mr Burke explained that this proposal represents a compromise between the European Commission which wanted to lift restrictions on feeding pure fish meal to ruminants and the European Parliament which objected to feeding non-vegetable products to ruminants which are natural herbivores. However, both parties agreed that fish meal did not pose a known TSE risk, unless it was contaminated with MBM. The ban on feeding fish meal to older ruminants would be maintained by labelling and

separation but is not seen as a TSE control measure. Members agreed this would not be a robust TSE control measure.

36. Members considered that if BSE testing of cattle, the specified risk material controls and high temperature and pressure processing of PAP continued then the risks of the relaxations to controls proposed to public health would remain very small and would prevent further epidemics of BSE in cattle. However, continuing BSE and vCJD surveillance was important in order to determine whether changes to controls may have had adverse effects, although because of the long incubation period of these diseases there may be a delay in detection of adverse effects.
37. A member suggested that it may help risk perception if the risks from relaxations to controls could be translated into the expected increase in number of vCJD cases, as was done for the relaxation of the over 30 months rule (OTM). It would be expected that the number of additional vCJD cases for relaxation of PAP regulations would be very small, and that the projected risk would be much smaller than that experienced during the peak of the BSE epidemic.
38. The Chair summarised the discussion noting:
 - given the low prevalence of BSE, the risks from the changes to controls proposed appear low to negligible. However, the impact of the changes should not be considered in isolation, as the BSE risks associated with one change may be magnified by other changes to controls.
 - it is extremely important that adequate surveillance is in place so that adverse effects from the changes to BSE or other TSE controls can be detected.
 - a statement would be produced.

ITEM 7 – HORIZON SCANNING (SEAC 99/5)

39. Due to a lack of time, this item was postponed to SEAC 100.

ITEM 8 – PUBLIC QUESTION AND ANSWER SESSION

40. The Chair explained that the purpose of the question and answer session was to give members of the public an opportunity to ask questions related to the work of SEAC. Mr Terry Singeltary (Texas, USA) had submitted a question prior to the meeting, asking: "*With the Nor-98 now documented in five different states so far in the USA in 2007, and with the two atypical BSE H-base*

cases in Texas and Alabama, with both scrapie and chronic wasting disease (CWD) running rampant in the USA, is there any concern from SEAC with the rise of sporadic CJD in the USA from "unknown phenotype", and what concerns if any, in relations to blood donations, surgery, optical, and dental treatment, do you have with these unknown atypical phenotypes in both humans and animals in the USA? Does it concern SEAC, or is it of no concern to SEAC? Should it concern USA animal and human health officials?"

41. A member considered that this question appeared to be primarily related to possible links between animal and human TSEs in the USA. There is no evidence that sCJD is increasing in the USA and no evidence of any direct link between TSEs and CJD in the USA. Current evidence does not suggest that CWD is a significant risk to human health. There are unpublished data from a case of human TSE in the USA that are suggestive of an apparently novel form of prion disease with distinct molecular characteristics. However, it is unclear whether the case had been further characterised, if it could be linked to animal TSEs or if other similar cases had been found in the USA or elsewhere. In relation to the possible public health implications of atypical scrapie, H-type BSE and CWD, research was being conducted to investigate possible links and surveillance was in place to detect any changes in human prion diseases. Although possible links between these diseases and human TSEs are of concern and require research, there is no evidence to suggest immediate public health action is warranted. The possible human health risks from classical scrapie had been discussed earlier in the meeting. Members noted that there are effective channels of discussion and collaboration on research between USA and European groups. Members agreed it is important that to keep a watching brief on new developments on TSEs.

ITEM 9 – UPDATE ON vCJD AND sCJD EPIDEMIOLOGY

42. Dr Richard Knight (NCJDSU) presented an update on the epidemiology of cases of sCJD and vCJD in the UK and elsewhere. Between May 1990 and October 2007, 944 cases of sCJD had been identified in the UK with a mean age at onset of 66 (range 15-94) years and mean age of death of 67 (range 20-95) years. There is no significant gender difference in sCJD incidence. There had been a trend towards an increasing number of cases over time to almost 80 cases per year in 2003; this increased trend had also been observed in other countries and was considered to be a result of better surveillance and diagnosis of disease. There has been a decline in number since 2003, but this may not be of

significance. The post mortem rate for sCJD referral is about 60%. The genotype distribution of sCJD cases was 64% MM, 18% MV and 18% VV at codon 129 of the prion protein gene.

43. Dr Knight explained that the total number of definite and probable vCJD cases in the UK up to November 2007 was 166, with four cases still alive. Three of out of four vCJD cases treated with pentosan polysulphate (PPS) had appreciably longer survival times, but it is not proven that this is the result of treatment. No statistically significant gender difference had been observed in vCJD cases. The age distribution of vCJD had not altered over the course of the UK epidemic, with the median age of death of 30 (range 14-75) years. Statistical analysis of the UK incidence of deaths from vCJD suggested the epidemic had peaked in 2000 with 28 deaths. There are three cases identified with onset in 2006 and four deaths in 2007. Geographical distribution of vCJD cases in the UK shows higher incidence in the North than South. All 146 vCJD cases tested to date are of the MM genotype.
44. Dr Knight explained that elsewhere in the world up to November 2007, 39 vCJD cases have been reported with 23 in France, four in the Republic of Ireland (RoI), three in the USA, two in the Netherlands, two in Portugal and single cases in Italy, Canada, Japan, Saudi Arabia and Spain. Infection is considered likely to have occurred in the UK in two RoI cases, two USA cases, one French case, the Japanese, and Canadian cases. One of the French cases had a history of possibly significant residence in the UK. One USA case is thought likely to have been exposed to infection in Saudi Arabia, rather than the USA.
45. Dr Knight explained that the Transfusion Medicine Epidemiology Review study had identified four instances of vCJD infection resulting from receipt of non-leucodepleted red blood cells donated by individuals who had subsequently developed vCJD. The donors developed clinical vCJD ranging from 17 months to 3.5 years after blood donation and this indicates that blood can be infective 3.5 years before the development of clinical disease. Clinical vCJD was identified in three recipients (all of MM genotype) between 6.5 and 8.3 years after receipt of blood. The fourth recipient, who died of non-neurological disease, with only lymphoreticular evidence of vCJD infection was of MV genotype.
46. In response to a question about the neuropathology of the vCJD case that died after receiving PPS, Dr Knight explained that no autopsy was undertaken.

47. A member asked about the reason for the increase in sCJD detection in the year up to 2003. Dr Knight replied that it was probably due to better awareness of the disease and the availability of better diagnostic methods such as cerebrospinal fluid testing and magnetic resonance imaging.
48. Mr Mark Noterman (Department of Health [DH]) asked whether the neuropathological referrals rate had increased after the Chief Medical Officer's letter to clinicians earlier in the year to remain vigilant about cases of neurological disease that could be related to prion disease. Dr Knight replied that there had been no subsequent significant increase in referral rate.

ITEM 10 – UPDATE ON NATA AND OTHER PREVALENCE STUDIES

49. Dr Jonathan Clewley (Health Protection Agency [HPA]) presented an overview of the testing methodology used and results from the National Anonymous Tonsil Archive (NATA). Up to September 2007, 45122 samples were tested using two different enzyme immunoassays (EIAs) with samples classified as reactive, high negative or negative based on the magnitude of the EIA signal obtained. Samples reactive in either EIA or repeatedly high negative in one or both EIAs were further analysed using investigatory western blot (WB) and immunohistochemical (IHC) tests. Samples were classified as positive, inconclusive or negative to a defined algorithm with samples classified as positive, indeterminant, or negative according to a defined algorithm. To be defined as a PrP^{Sc} positive, a sample would have to be specifically reactive in either confirmatory test (WB or IHC). Indeterminant samples were those that had undergone WB and IHC testing, and could not be defined as positive samples but were worthy of further research investigations. Negatives samples were those that did not conform to the above criteria.
50. Dr Clewley explained that the performance of the two EIAs had been assessed by validation studies with tonsil samples spiked with brain or spleen from vCJD cases, with tonsil samples from sheep with classical scrapie and with tonsil samples from clinical vCJD cases over a range of dilutions. The results suggested that the limit of detection of PrP^{Sc} in tonsils on EIA testing was around 0.1-1% of the level found in clinical vCJD. The sensitivity of the WB tests were within a similar range.
51. Dr Clewley gave an overview of the test results. About 400 samples had been selected for investigatory confirmatory analysis on the basis of the EIA results. No samples were clearly reactive

in both EIAs, and only one gave an EIA reading that was defined as reactive by one and high negative by the other. Eight gave EIA readings that were defined as high negative by both tests. However, none of these samples were also IHC reactive or gave the characteristic PrP^{Sc} profile by WB. Two samples showed a single band by one WB test method, but not by another. These two were negative by IHC.

52. A member noted that the EIA, western blot and IHC tests used different antibodies and the testing strategy should therefore be able to confirm true PrP^{Sc} positive results and enable falsely reactive results in any one test to be ruled out. Although a number of samples gave reactive results in one test, none had been reactive in both tests. However, it is not known if PrP^{Sc} in tonsil tissue from subclinical vCJD patients could remain undetected. Dr Clewley explained that control samples of hamster scrapie brain homogenate were incorporated into the testing protocol to confirm that the assays would detect PrP^{Sc}, and that the validation studies referred to above established that the EIAs will detect low amounts of PrP^{Sc}. The quantity of tonsil material available from vCJD cases was too limited to be used as control material in the screening tests. Also as no tonsil material is available from subclinically infected individuals the sensitivity of the test to detect PrP^{Sc} in the tonsils of such individuals cannot be assessed directly. However, the sensitivity analyses conducted with dilutions of tonsils from vCJD cases indicates that the EIAs should detect PrP^{Sc} at much lower levels than found at the clinical stage of vCJD. When tonsils are prepared for testing the germinal centre tissue is dissected for testing as this tissue contains the highest concentrations of PrP^{Sc}.
53. Members asked whether any of the nine samples that had given repeat reactive or high negative results in EIAs, or the two samples with a single WB band had been submitted to mouse bioassays. Dr Noel Gill (HPA) explained that most of these samples were from individuals not considered to be in the most vulnerable birth cohort of the population and that no decisions had been made on submitting samples for bioassays.
54. Members asked whether the tests could be applied to the PrP^{Sc} positive appendix tissue collected by Hilton *et al.* (2004)⁶ to assess whether the tests were sensitive enough to detect PrP^{Sc} in samples from individuals with a subclinical infection. Dr Clewley explained that the remaining appendix tissue was in the form of wax blocks, which is not suitable for EIA. Professor Gill added that a study to

⁶ Hilton *et al.* (2004) Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol.* 203, 733-739.

test 10 000 NATA samples by IHC had begun. Members suggested that the IHC method used should be as close to the Hilton *et al.* method as possible.

55. A member presented an epidemiological analysis of the data. Most deaths from vCJD are in the 1961-1985 birth cohort. The three PrP^{Sc} positive samples found by Hilton *et al.* were from 10278 appendix samples tested within this birth cohort. As zero PrP^{Sc} positive samples had been found in 9348 NATA samples tested from this birth cohort, the two surveys gave statistically consistent results. The results from testing of NATA samples from later birth cohorts supports assumptions about the lower prevalence of infection in post 1985 birth cohorts. Professor Gill noted that NATA samples from the 1961-1980 birth cohort were collected on average about five years later than the appendix samples collected by Hilton *et al.*, therefore it is possible that the tonsil testing may be more sensitive than the appendix testing as PrP^{Sc} may have had more time to accumulate in infected individuals in this birth cohort.
56. Professor Gill explained that testing is proceeding at a faster rate than collection and the rate of tonsil collection could not be increased. It is expected that 100 000 tonsils samples would be tested by September 2009 of which 25 000 would be from the 1961-1985 birth cohort.
57. Members noted that the testing approach might be questioned if no positive samples were found in 25 000 samples from the 1961-1985 birth cohort. Dr Peter Bennett (DH) suggested that it may be helpful if SEAC could consider the implications of such a scenario.
58. Members considered it very important that a post mortem tissue archive be implemented to allow assessment of the prevalence in the older population, since many tonsil samples are collected from younger individuals, and to provide reassurance about the findings from NATA. Professor Gill explained that ethical approval for a post mortem tissue archive had been obtained. A pilot survey is planned. However, as a result of changes underway in the coronial system there appears to be reluctance amongst coroners to collaborate in a large-scale post mortem archive.

ITEM 11 – RE-ASSESSMENT OF THE POTENTIAL RISK OF vCJD TRANSMISSION VIA DENTISTRY (SEAC 99/7)

59. Dr Bennett and Dr Peter Grove (DH) presented findings of an interim assessment examining the risk that vCJD may be transmitted via dental procedures. As there is a lack of substantial

data with which to accurately quantify many of the key parameters in the risk assessment, plausible ranges for parameters were established to take account of the often large uncertainties in the data. The key areas of uncertainty are infectivity in dental and oral tissues of patients incubating vCJD, the level of protein residues on dental instruments following decontamination, the efficacy of autoclaving, the current prevalence of vCJD infection in the population, and the epidemiology of vCJD. These uncertainties strongly influence the quantification of the risk.

60. It was explained that many plausible scenarios built up using ranges for each of these factors suggest that dental transmission may have no detectable effect on the course of the vCJD epidemic. However, there are some scenarios which include a combination of pessimistic assumptions as regards the infectivity of dental/oral tissues and the effects of instrument decontamination which suggest that there could be some hundreds of vCJD transmissions per annum via dentistry, albeit against a background of many thousand existing subclinical vCJD infections, or where dental transmission could generate a self-sustaining reservoir of vCJD infection within the population. Should a large proportion of secondary transmissions result in subclinical infections, either never developing into clinical disease or doing so over an extended time-scale, and such infections are infectious, the likelihood of a self-sustaining epidemic increases. The proportion of individuals that may be infected from having consumed BSE contaminated food or from human to human transmission of vCJD that may enter such a subclinical carrier state is unknown. Research to address the key uncertainties is on-going and new data would enable some of the assumptions underpinning these scenarios to be revised.
61. The committee welcomed the risk assessment, acknowledging it had been developed in collaboration with a scientific reference group of independent experts. Studies to address the scientific uncertainties were considered important, particularly infectivity studies on human oral and dental tissues from vCJD patients.
62. A member suggested that following secondary transmission, the agent may adapt to become infectious to all prion protein genotypes. Dr Grove noted that since the risk assessment considers four scenarios ranging from one in which no secondary infection develops into clinical disease to one in which everyone who is infected develops clinical disease, this possibility is considered.

63. Members noted that there were two obvious precautionary measures that could be put in place to dramatically reduce the potential risk of vCJD transmission via dental procedures: making endodontic files and reamers single use, which was implemented in April 2007 and improving instrument decontamination using current technologies. A 0.5 – 1.0 log reduction in infectivity from improved decontamination practice could remove the risk of a self sustaining epidemic. It is very important, therefore, that DH ensures dentists do adopt good practice throughout the profession and that this is audited. Introduction of consistent decontamination practices would also reduce the observed variability of instrument contamination, and thus reduce the risk of local outbreaks of transmission.
64. Mr Barry Cockcroft (Chief Dental Officer, DH) noted that the effect of the guidance on making endodontic files and reamers single use had been included in the risk assessment. There is good evidence that dentists are adhering to the guidance. A survey by DH Regional Directors of Public Health could not find any dentists who are unaware of the Chief Dental Officer's Professional Letter advising that files and reamers should be treated as single use only, and dental instrument suppliers have reported that sales of files and reamers have increased dramatically since the guidance was issued. A draft Health Technical Memorandum would be issued for consultation in early 2008 designed specifically for dental practitioners and their staff as a comprehensive guide to best practice. An audit tool will be available to help dentists assess their own compliance with the guidance and to enable DH to assess whether new guidance is working in practice. Dental nurses will now also be regulated and registered with the General Dental Council.

ITEM 12 – ANY OTHER BUSINESS

65. The Chair noted that Dr Matthews and Professor John Wilesmith would be retiring in the near future and thanked them for the tremendous support that they have given SEAC and its Subgroups over many years. A small gift of thanks had been sent to them.
66. The Chair closed the meeting, thanking all those that had presented information to the committee and all those that attended the meeting.