



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Minutes of the 94th meeting held on 21st September 2006

Hilton Hotel
4 Lanyon Place, Belfast BT1 3LP

- Members: Professor C. Higgins (Chair)
Professor D. Brown
Professor N. Hooper
Mr. P. Jinman (Deputy Chair)
Professor J. Manson
Ms. D. McCrea
Professor G. Medley
Professor J. Nicoll
Dr. P. Rudge
Professor A. Williams
- Assessors: Dr. A. Douglas (DARDNI)
Dr. A. Gleadle (FSA)
Dr. D. Hughes (DH)
Dr. M. Simmons (NAW)
- Technical Experts: Mr. P. Burke (Defra)
Dr. I. Hill (FSA)
Dr. J. Stephenson (DH)
- SEAC Secretary: Miss K. Richards
- Secretariat: Dr. T. Barlow
Dr. D. Cutts
Dr. N. Ebenezer
Dr. P. Keep
Dr. C. Ravirajan
- Also in attendance Dr. C. Bonner (DHC, Republic of Ireland)
Dr. R. Eglin (NBS)
Dr. R. Knight (NCJDSU)
Dr. P. Minor (NIBSC)
Dr. J. Parry (HPA)

ITEM 1 – CHAIR’S INTRODUCTION

1. The Chair welcomed everyone to the 94th meeting of SEAC, the first in Northern Ireland. He welcomed Dr Colette Bonner (Deputy Chief Medical Officer, Department of Health and Children, Republic of Ireland) to the meeting. The Chair explained that each year SEAC holds a meeting in a devolved administration to make the committee’s work more accessible to the public. He thanked the Department of Agriculture and Rural Development, Northern Ireland (DARDNI) for hosting the meeting and a dinner for SEAC members the preceding evening, and Mr Pat Toal (DARDNI) and his colleagues for working with the secretariat to help organise this meeting.
2. The Chair explained that the agenda for the open session consisted of a number of short items as well as discussion items. This was because a considerable amount of SEAC’s current work is being conducted by the SEAC Sheep and Epidemiology Subgroups, both of which would meet in the next two months. Reports from these Subgroups would be discussed at a future SEAC meeting. The agenda also included a horizon scanning session to allow Government departments to outline the transmissible spongiform encephalopathy (TSE) related issues on which they are likely to seek SEAC’s advice in the future. The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) would also outline issues from its perspective. In addition, the meeting would include a public question and answer session. Two questions had been submitted in advance and additional questions from the floor were welcomed.
3. The SEAC 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 TSE policy may be invited to contribute to discussions. A short summary of the discussions and a video recording of the meeting would be available on the SEAC website next week.
4. A list of website addresses of recently published reports relevant to TSEs and copies of the presentations to be made during the course of the meeting had been tabled. In addition, the two questions submitted for the public question and answer session and the Department of Environment, Food and Rural Affairs

(Defra) TSE Progress Report for 2005¹² had been tabled. The TSE Progress Report records the decline in cases of bovine spongiform encephalopathy (BSE) and progress in control of the disease. This is the last progress report in this format, this information will continue to be published in Defra's Annual Departmental Report and the Chief Veterinary Officer's Annual Report.

5. Following the departure of Mrs Eileen Lawrence (Department of Health [DH]), Dr Darren Hughes is acting SEAC assessor for DH.
6. The papers for SEAC 94 were sent to the committee and government officials by post and email. It is proposed that in the future, the committee will continue to receive papers by post and email while government officials will receive papers by email only.
7. The next SEAC meeting will be held on Thursday 7th December 2006 at the Royal Horticultural Halls, Westminster, London.
8. Apologies for absence had been received from Mr John Bassett, Dr Jacky Chambers and Professors Corinne Lasmézas and Margaret Stanley. However, comments on the issues under discussion had been received from members who could not attend the meeting.
9. 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 to comply with the SEAC Code of Practice.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 93 (SEAC 94/1)

10. The minutes of the open session of SEAC 93 were agreed as a correct record, subject to the following amendments:
 - paragraph 10, fourth bullet point, change “...to consider post mortem testing as a means of obtaining better data on the prevalence, age and genotype distribution of vCJD in the UK population...” to “...to consider the best way, including post mortem testing, of ascertaining the prevalence, age and

¹² Defra (2006) Transmissible Spongiform Encephalopathies (TSE) in Great Britain 2005 – a progress report.

genotype distribution of subclinical vCJD in the UK population...

- paragraph 11, second bullet point, change “...there was no evidence CWD...” to “...there was no evidence that CWD...” and change “...through natural means.” to “...through non-experimental means.”
- paragraph 13, first sentence, change “...red and white tailed deer...” to “...red deer and white tailed deer...”
- paragraph 18, second sentence, change “...distinct differences had been found...” to “...distinct differences in the neuropathological phenotype had been found...”
- paragraph 25, last sentence, change “The EU audit population is 43 million cattle.” to “The EU adult cattle population is 43 million.”
- paragraph 38, second bullet point, change “...and bovinised or humanised mice with BSE or vCJD, respectively.” to “and bovinised mice with BSE or humanised mice with vCJD or sCJD.”
- paragraph 46, first sentence, change “...to define a single strain of TSE in sheep.” to “...to define TSE cases in sheep distinct from classical scrapie.”
- paragraph 46, second sentence, change “However, there are some differences in the phenotype of atypical cases of BSE in cattle therefore, it is possible that more than one strain of TSE agent may be involved.” to “As there are some differences in the phenotype of TSE cases in cattle that appear different from BSE, it is possible that more than one strain of TSE agent may be involved.”

11. The Chair asked members to submit comments on the reserved business session of SEAC 93 by email.

ITEM 3 – CURRENT ISSUES

12. SEAC was informed about the following issues:

- The publication of a report by the Scientific Committee on Emerging and Newly Identified Health Risks¹³ following a public consultation. The report had been revised in light of comments from SEAC for example, to emphasise that specific measures had been taken in the United Kingdom (UK) to reduce the potential for transmission of variant CJD (vCJD)

¹³European Commission Scientific Committee on Emerging and Newly Identified Health Risks (2006) Safety of Human-derived Products with regard to vCJD http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/scenihhr_cons_02_en.htm

via blood transfusion and to highlight the potential for transmission of vCJD via surgery and dentistry.

- An interim report from the Implementation Review Group on the System for BSE Testing of Cattle Aged Over Thirty Months concluding that the testing system had worked satisfactorily since its introduction. Two cases of BSE had been confirmed to date and no ineligible animal had entered the food supply. The report is available on the Food Standards Agency (FSA) website¹⁴.
- Dr Alison Gleadle (FSA) informed the committee about an investigation into Over Thirty Month BSE testing controls relating to the authenticity of brain samples from two cattle aged over thirty months. Operations at the meat plant have been suspended pending further investigations. Further information is available on the FSA website¹⁵.
- The Clinical Governance Advisory Group (CGAG), an independent group convened to advise DH on the appropriate counselling and care for individuals defined as 'at risk from vCJD for public health purposes'. CGAG will meet on the 10th October 2006 to finalise its report for expected release in November 2006.
- The Chair asked members to comment on the membership and terms of reference of an expert group to be convened by the Health Protection Agency (HPA), which had been tabled. This group would consider the best way of ascertaining the prevalence, age and genotype distribution of subclinical vCJD in the UK, following the SEAC recommendation¹⁶. It was anticipated that the Group would meet twice by December 2006 and issue a report in January 2007. The Chair noted that at a recent meeting of the chairs of committees that advise DH on TSE issues, it was agreed that ascertaining the prevalence of vCJD infection was the top research priority. The Chair commented that he was pleased this issue was now being progressed by the HPA. He was also pleased he has been given the opportunity to discuss the expert group with its Chair, Professor Montgomery, next week where he can pass on SEAC's priorities. Members suggested that the key issue was to ascertain the prevalence of vCJD in the UK

¹⁴<http://www.food.gov.uk/aboutus/ourboard/boardmeetings/boardmeetings2006/boardmeeting130706/agenda13jul06>

¹⁵<http://www.food.gov.uk/news/newsarchive/2006/aug/srmupdate0708>

¹⁶<http://www.seac.gov.uk/statements/state260106.htm>

population as quickly and reliably as possible. The remit of the Group should therefore include other avenues to ascertaining prevalence, as well as the collection and testing of material from autopsies, including the collection and testing of material from tissue or organ donations. Analysis of this material may provide gross estimates of the prevalence of vCJD infection. Members also suggested that the 30 000 samples collected to date for the National Anonymous Tonsil Archive (NATA) be tested with urgency, as this may provide a good indication of the prevalence of subclinical vCJD. Members suggested that the Group appeared to be focused on detail, such as method of sample collection, and may require additional expertise to fully address the ethical and legal implications of tissue collection and testing. The Chair stressed that the principal objective of the Group should be to determine the approach to provide the best possible and most rapid estimate of the prevalence of vCJD infection. This may or may not include testing of post mortem tissues¹⁷.

ITEM 4 – UPDATE ON TSE TESTING

13. Dr Alastair Douglas (DARDNI) presented data on the TSE testing of cattle, sheep and goats in Northern Ireland (NI) since 2000. BSE and scrapie testing was carried out by the Veterinary Science Division using the BioRad TeSeE as a rapid screening test, with confirmation of positive results by histopathology, immunohistochemistry and western blot. Since 2000 the number of animals tested had increased substantially, with an overall decline in BSE incidence observed since 2000. Seventeen BSE cases born after the reinforced ban had been identified in surveys in the years 2000 to 2005. Since BSE testing for cattle aged over thirty months was introduced in November 2005, about 89 000 animals had been tested, with no BSE cases found. TSE surveys of sheep from fallen stock and at abattoirs as well as surveys of fallen stock goats, identified one scrapie case in a sheep in the years 2002 to 2004. Subsequent expansion of scrapie testing, to include testing of scrapie monitored and scrapie infected flocks, had increased the numbers of TSE cases detected with 8 and 10 cases in sheep identified in surveys in 2005 and 2006, respectively.

¹⁷ Note added following the meeting: the SEAC Chair, Chair of the SEAC epidemiology subgroup, and Professor Noel Gill (HPA) agreed that the present expert group would focus on post-mortems, and that the SEAC Epidemiology Subgroup, at its next meeting, would take an overview of all possible methods for ascertaining prevalence, including post-mortem. The Chair wrote to the Chair of the Epidemiology Subgroup to this effect on 02/10/06.

14. A member asked whether the testing methods used could distinguish classical and atypical scrapie cases. Dr Douglas explained that the Community Reference Laboratory examined all the NI TSE cases for this purpose and no atypical scrapie cases had been identified to date.
15. SEAC agreed that these data were in line with those expected for the continued decline of the BSE epidemic.

ITEM 5 – CJD UPDATE

16. Dr Richard Knight (NCJDSU) provided an update on the epidemiology of cases of sporadic CJD (sCJD) and vCJD in the UK and elsewhere. Between May 1990 and June 2006, 845 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 phenomenon had also been observed in other countries and was considered to be a result of better ascertainment. Fewer cases were identified in the UK in 2004 compared to 2003 and 2005 but this finding may not be significant. The genotype distribution of sCJD cases was 64% methionine (M) M, 18% M valine (V) and 18% VV at codon 129 of the prion protein gene.
17. The total number of definite and probable vCJD cases in the UK up to September 2006 was 162, with six cases still alive. Two of these are considered to have been infected by blood transfusion rather than a dietary route. 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 28 (range 12-72) years. The median duration of clinical vCJD was 14 (range 6-40) months. Statistical analysis of the UK incidence of deaths from vCJD suggested the epidemic had peaked in 2000 with 28 deaths. All 141 vCJD cases tested to date are of the MM genotype. Elsewhere in the world up to September 2006, 34 vCJD cases have been reported with 20 in France, four in the Republic of Ireland (RoI), two in the USA, two in the Netherlands and single cases in Italy, Canada, Japan, Saudi Arabia, Spain and Portugal. The clinical, pathological and prion protein gene PrP codon 129 genotype of all these cases is similar to that of UK cases. Infection was likely to have occurred in the UK in two RoI cases, both USA cases, one French case and the Japanese and Canadian cases.

18. Dr Knight explained that evidence from experiments to compare BSE transmission to bovinised and humanised mice suggested a significant barrier to transmission of BSE between cattle and humans. There appears to be much less of a barrier between humans, suggesting that secondary transfer from human to human may be relatively efficient. This is borne out by the three recent blood transfusion associated cases of vCJD. However, although all clinical cases of vCJD that have been genotyped are of the MM genotype, there is evidence that cases of non-MM genotypes should be expected. Infected individuals of non-MM genotypes may have longer incubation periods, subclinical infections and, or a different clinico-pathological phenotype. Experiments on the transmission of vCJD to humanised mice of the MM, MV or VV genotype suggested that susceptibility to vCJD was highest in MM, lower in MV and lowest in VV¹⁸. Mice of MM and MV genotypes showed similar rates of brain involvement, however differences in neuropathology were observed between the three genotypes. The incubation period was shortest in MM mice and a higher rate of subclinical disease was found in MV and VV mice.
19. Dr Knight explained that data from the UK appendix and tonsil study¹⁹ provided further evidence for the existence of subclinical vCJD infections. In this survey, three out of 12 674 samples had tested positive for abnormal prion protein (PrP^{Sc}), indicating a prevalence of 237 (95% confidence interval 49-692) cases per million. An extrapolation of these data suggest 3 808 (95% confidence interval 785-11 128) people could be infected out of approximately 16 million in the 10 to 30 year old age group. However, the actual number of clinical cases of vCJD observed in the 10 to 30 age group was 102, and in decline. The discrepancy in observed and predicted cases in the 10 to 30 year age group could be due to subclinical infections. Whether these individuals will eventually develop vCJD clinical disease, with a longer incubation period, is unknown. Importantly, two out of the three positive appendix samples were VV, a much higher proportion than the 11% of VV individuals in the UK population. If it is assumed that the third positive appendix is non-VV, statistical analysis indicates a prevalence ratio of VV to non-VV of 18:1. If the third positive appendix is MM, then the VV:MM prevalence ratio is 8:1. This suggests that, although VV may have the longest incubation period, it may be most susceptible genotype. However, this seemed counterintuitive and not consistent with data from

¹⁸ Bishop *et al.* (2006) Predicting susceptibility and incubation time of human-to-human transmission of vCJD. *Lancet Neurol.* 5, 374-375

¹⁹ Hilton *et al.* (2004) Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J. Pathol.* 203, 733-739.

humanised mice, thus there may be an important unidentified factor involved. Although the downward trend in vCJD clinical cases is reassuring, it is possible that subclinical infections may be more widespread. Further peaks in vCJD cases could occur, however the timescale in which these peaks could occur is uncertain. It is therefore very important to ascertain the prevalence of subclinical infection in the UK population.

20. Dr Knight explained that three blood transfusion associated vCJD cases had been identified through the Transfusion Medicine and Epidemiological review (TMER)²⁰. The first case (MM), developed vCJD 6.5 years after receiving non-leucodepleted red blood cells (RBC) from a donor, who themselves developed vCJD 3.3 years after donation²¹. The second case (MM), developed vCJD 7.8 years after receiving non-leucodepleted RBC from a donor, who themselves developed vCJD 1.8 years after donation. The third case²²(MV) died of a non-neurological illness five years after receiving non-leucodepleted RBC from a donor, who themselves developed vCJD 1.5 years after donation. PrP^{Sc} was detected in the spleen of this recipient, with no other clinical or neuropathological evidence of vCJD infection. Statistical analysis indicated that the chances of the three recipients having developed vCJD through consuming BSE infected meat was one in a thousand million, therefore it could be concluded that transmission had occurred via blood transfusion.
21. The TMER also identified 66 individuals who received blood from donors who later developed vCJD. Out of these individuals, 42 recipients have died and of those still alive, seven have survived over 10 years after receiving the donation, without developing vCJD. There were 25 blood donations from 11 individuals that subsequently developed vCJD that were used for plasma fractionation, however no cases of vCJD have occurred in recipients of plasma.
22. In the reverse TMER study, seven vCJD cases were identified as having received blood from 121 identified donors, two of which were known vCJD cases. If these two cases are excluded, together with a third case, because of the small amount of time between the onset of disease and the timing of the transfusion, four cases remain. One of these recipients received two

²⁰ Hewitt *et al.* (2006) Creutzfeld-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review Study. *Vox Sang.* 91, 221-230.

²¹ Llewelyn *et al.* (2004) Possible transmission of variant Creutzfeld Jakob disease by blood transfusion. *Lancet* 363, 417-421.

²² Peden *et al.* (2004) Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 364, 527-529.

transfusions in the same year and developed clinical vCJD four or five years post transfusion. In a second recipient of two blood transfusions, the onset of vCJD was 17 years after the first transfusion and between six and seven years after the second transfusion. The two other recipients each received one transfusion with the onset of vCJD at around six and 14 years following transfusion.

23. The Chair noted that although the incidence of clinical vCJD was reducing, recent evidence suggested that there may be a substantial number of subclinical carriers that could potentially give rise to secondary transmissions. Therefore it was very important to know the prevalence of subclinical vCJD.
24. A member asked how the incidence of vCJD and BSE compare in other countries, relative to that of the UK. Dr Knight indicated that the numbers of BSE and vCJD cases in some countries correlate poorly. In addition, in some countries the historic incidence of BSE is not well known or uncertain and numbers of vCJD cases are too small to make meaningful comparisons.
25. A member noted that the genotype of the PrP^{Sc} positive samples from the appendix and tonsil survey raised many questions. These include whether individuals of the VV genotype were protected from clinical disease, whether PrP^{Sc} resided in the appendix rather than in the brain in these individuals and whether these individuals were themselves infectious. Further studies were needed to answer these questions. A member asked whether transmission studies using the PrP^{Sc} positive appendix material were underway. Dr Knight was not aware if transmission studies had begun on this material.
26. In relation to studies in humanised mice inoculated with vCJD, a member noted that the incubation time times could not be equated with susceptibility to vCJD.
27. A member asked if the genotype of the transfused patients surviving for 10 years after receiving vCJD infected blood was known. Dr Knight indicated this was not known and agreed these are important data.
28. Regarding the possible barrier to transmission of BSE from cattle to humans, a member noted that this could be due to inefficient entry or inefficient replication of the BSE agent in humans and these possibilities are under investigation.

29. Members agreed it was important to continue surveillance to be able to detect the onset of secondary epidemics of vCJD. It was noted that there may be periods of a number of years with few or no cases of vCJD, before an increase in cases may be observed.

ITEM 6 – REPUBLIC OF IRELAND PERSPECTIVE ON TSEs

30. Dr Bonner provided an overview of the management of TSEs in the RoI. The first case of BSE was diagnosed in 1989, classified as a notifiable disease in 1989 and a ban on feeding mammalian meat and bone meal (MMBM) to ruminants and restrictions on the import of cattle and cattle products from the UK introduced in 1990. After the identification of the first case of vCJD in the UK in 1996, the Food Safety Authority of Ireland (FSAI), National CJD Committee and National CJD Surveillance Unit (in the RoI) were established. Enhanced feed and specified risk material controls were introduced to protect the food chain in 1996 and 1997, which are monitored and audited by the FSAI. Surveillance shows a decline in the number of BSE cases over the past four years, with most cases currently from cohorts born before the introduction of the enhanced feed controls.
31. Dr Bonner explained that the National CJD Committee was set up to advise the Health Minister on issues such as surveillance, scientific developments and research, media communication and clinical risk management. The committee had advised that individuals that lived in the UK for one year cumulatively between 1980 and 1996, received a blood transfusion since 1980 or received surgery or root canal treatment in the UK since 1980 be deferred from donating blood. In addition, plasma has been imported to the RoI from the United States of America (USA) since 2002. The National CJD Committee is currently being reconfigured as the National TSE Committee and a Critical Incidents Panel is being established to provide advice on the management of incidents relating to possible transmission of human TSEs.
32. Dr Bonner explained that the National CJD Surveillance Unit undertakes surveillance, diagnosis, notification and epidemiological investigation. The Unit is monitoring 45 haemophiliacs classified as at risk of vCJD, who received contaminated blood products and one person who received blood from an individual, who later developed vCJD in 2005. There have been four cases of vCJD in the RoI. Two cases were attributed to exposure to BSE whilst resident in the UK, however two cases have no history of travel to the UK, blood transfusion or surgery.

33. A member asked whether the exclusion criteria of one year's cumulative residence in the UK for blood donor referral was stringent enough, given a Japanese case of vCJD was presumed to have been infected after one month's residence in the UK. Dr Knight noted that classification of this case as UK origin had been difficult, as the probability of infection occurring during such a short visit to the UK was very low. However the probability that exposure to BSE had occurred in Japan was considered even lower. In Japan, all individuals who have spent a day or more in the UK are deferred from donating blood. Members noted that the current RoI deferral policy, although less stringent, had resulted in a thirty per cent drop in available blood donors thus, more stringent measures would adversely affect the supply of blood.
34. The Chair thanked Dr Bonner and explained that SEAC would look to build links with the National TSE Committee.

ITEM 7 – HORIZON SCANNING (SEAC 94/3)

35. The Chair explained that this agenda item had been included to give the assessors from DH, FSA and Defra and as well as the NCJDSU an opportunity to provide SEAC with brief overviews of topics that might require the committee's consideration in the future.

Defra

36. Mr Patrick Burke (Defra) explained that the European Commission (EC) TSE Roadmap was last discussed at SEAC 93. There had been no developments since, as many of the proposals depend upon the European Council agreeing amendments to the European TSE Regulation. The European Council is expected to consider the amendments in late October 2006. TSE surveillance of deer, as proposed in the Roadmap, was likely to begin later in the year. Should positive cases be identified, Defra may need advice from SEAC. The TSE Roadmap contains proposals for the relaxation of the total feed ban. Two aspects of this include a tolerance level for low levels contamination of ruminant feed with fish meal and the feeding of fish meal to calves. Defra felt it would be useful to have clarification from SEAC as to whether they have TSE-related concerns about feeding pure fishmeal to ruminants or about the ability to detect contamination of fishmeal with mammalian meat and bone meal (MMBM) using current tests. If SEAC was solely concerned about the MMBM detection aspects, Defra may ask SEAC to comment on the results of a proposed EC ring-trial to assess the sensitivity of methods to detect low levels of MMBM

contamination in fishmeal. Defra may also consult SEAC on a proposed European Commission report on fishmeal supply routes and the potential for contamination.

37. Mr Burke explained that surveillance of sheep had been enhanced by the EC, in light of the unusual TSE test results from two French and one Cypriot sheep earlier in 2006. The EC have committed to review the targets at the end of 2006 and Defra hopes that the targets will be reduced in early 2007.
38. Mr Burke mentioned that Defra is currently looking at the balance of costs and responsibility in line with its Animal Health and Welfare Strategy. A public consultation is expected later in the year. Defra will maintain its TSE research but a progressively managed reduction in funding is planned in line with the Department's priorities and policy responsibilities. Defra is conscious of recommendations to maintain core expertise in TSE science. Future research proposals may focus on the provision of evidence in relation to proposed changes to control measures. Defra has funded the development of a BSE risk model that assesses the risk of BSE control scenarios in terms of the infectivity consumed by the population of Great Britain (GB). The model is currently undergoing peer review. Subject to agreement of SEAC, it is proposed that the model be considered by the SEAC Epidemiology Subgroup in November 2006.

FSA

39. Dr Gleadle noted that FSA would also seek advice from SEAC on proposals arising from TSE Roadmap, in particular on modifications to specified risk material (SRM) controls. FSA is currently reviewing BSE controls relating to harvesting head meat from cattle. Currently head meat is harvested in abattoirs, however it is possible to apply a derogation under European Union (EU) law to allow harvesting in cutting plants. The UK has not applied for this derogation due to concerns about the risk of cross-contamination. The BSE risk model would be used to assess the potential changes in infectivity entering the food chain, as a result of allowing head meat harvesting at cutting plants. FSA would also like the SEAC Epidemiology Subgroup to comment on the construction of the BSE risk model. The results from the model would inform future policy decisions on supervision levels of head meat controls, should FSA allow head meat harvesting at cutting plants. FSA is also reviewing supervision levels of SRM controls at abattoirs, including an assessment of the change in risk resulting from modifications to supervision levels, and would wish SEAC or,

with the committee's agreement, the SEAC Epidemiology Subgroup to consider this risk assessment.

40. Dr Gleadle explained that FSA will continue to develop the contingency policy, should BSE be found in sheep. The current policy involves a graduated response, with increasing levels of control proposed depending on the number of unrelated cases of BSE in sheep that might be identified. FSA would be asking for advice from SEAC on the criteria for determining whether cases of BSE are related, should more than one case of BSE be identified in the national sheep flock, and on the appropriate level of surveillance should BSE be found in sheep. SEAC would also be consulted on the emerging science and contingency plans under development in relation to atypical scrapie. FSA would continue to maintain a watching brief on chronic wasting disease in deer and may wish SEAC to comment on its project examining the transmissibility of BSE to deer.

DH

41. Dr Hughes explained that DH and HPA have developed a formal project plan of work to ascertain the prevalence, age and genotype distribution of subclinical vCJD with DH owning the project and HPA managing the project. In light of the committee's discussion under item three, the remit of the working group on prevalence would be refocused to examine the best way of ascertaining the prevalence of subclinical vCJD. SEAC will be requested to help shape the working group on prevalence and kept informed on the deliberations of the group. SEAC may be asked to consider re-evaluated risk assessments on secondary vCJD transmission, in light of new data on prevalence.
42. Dr Hughes explained that, in October 2006, an independent advisory group established by the HPA, will examine data on rapid screening tests to determine the most appropriate method to test NATA samples. This advice may provide an indication of the likely timescale for testing NATA samples. SEAC will be asked to provide advice in relation to protocols for the evaluation of rapid ante mortem diagnostic tests for subclinical vCJD and new decontamination technologies for surgical instruments. The committee will also be asked to comment on the recommendations made in the CGAG report that would be released later in the year.

NCJDSU

43. Dr Knight explained that NCJDSU is considering how it may identify new cases of human illness should they arise from exposure to atypical scrapie or TSE cases in cattle that appear different from BSE and to examine whether, as has been suggested by some, there are links between sCJD and atypical scrapie. He noted that the possibility of vCJD infection in individuals of non-MM genotypes and that these individuals may present with a different clinical phenotype, were particular areas of uncertainty in relation to the vCJD epidemic. As the incubation period of human TSEs was long, continued surveillance was very important to identify new types of TSE and to identify potential routes of secondary transmission. Evaluation of the sensitivity and specificity of ante mortem blood tests for subclinical vCJD and the appropriate use of blood samples from vCJD cases was also of importance. It is likely that very large numbers of false positive results would arise from blood tests and it would be very important to consider the implications and handling of the results, prior to the introduction of blood testing.

Discussion

44. The Chair explained that Professor John Collinge (National Prion Clinic [NPC]) had been invited to contribute to the horizon scanning session, however he was unable to attend. However, Professor Collinge had personally informed the Chair that the NPC had partially characterised a number of mouse and human genes that appear to modify the incubation period and susceptibility to TSEs. Thus, it was possible that the clinical cases of vCJD identified to date were in individuals from a group that are genetically the most susceptible to this disease and further, possibly larger, numbers of cases might appear in the future in other genetic groups. A member noted that the prion protein gene is the major gene influencing susceptibility to TSEs. Although other genes may modify susceptibility to infection, they may have relatively small, but possibly, additive effects. Professor Collinge had suggested that some of the genes identified had substantial effects on the susceptibility to infection. Members considered it important to review these data when published. Dr Knight noted that EU funded projects were examining the existence of such modifier genes, using large numbers of subjects.
45. A member suggested that testing of NATA samples should begin immediately. Dr Hughes responded that testing would begin as

soon as an appropriate rapid test had been evaluated and validated.

46. In response to a query about cost sharing and TSE testing, Mr Burke explained that Defra was considering options for the sharing of the costs of TSE surveillance with industry and proposals would be issued for consultation.
47. A member suggested that defining the clinical signs of atypical scrapie would be important for clinical diagnosis of cases. Mr Burke explained that the low numbers of clinical cases that had been identified to date made this definition difficult. A member noted that cases of atypical scrapie had been identified in the closed experimental flock at the Institute of Animal Health and these animals were under close study. It was noted that the diagnosis of relatively rare diseases was difficult. It was explained that currently veterinarians were trained to identify abnormalities in behaviour and in steps to take to reach a definitive diagnosis. Thus, animals in the field with a clinical disease would be recognised but not necessarily as cases of atypical scrapie.
48. The Chair suggested that departments consider how best to conduct risk assessments to inform the possible relaxation of regulations. The approach taken to relax the Over Thirty Month Rule provided a good model. In addition, it was important that SEAC be kept informed of new research findings related to TSEs as they emerge.

ITEM 8 – PUBLIC QUESTION AND ANSWER SESSION

49. 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. He reminded everyone that the committee's remit is to provide scientific advice on TSEs. The committee does not make risk management or policy decisions on behalf of Government. Such questions would be referred to officials from the relevant Government department.
50. Mr Kieran Alcock (member of the public, RoI) submitted two questions in advance of the meeting. He asked whether bone meal produced in the 1980s and 1990s was contaminated with BSE and if so, what were the implications for public health from exposure to non-agricultural fertiliser containing such bone meal.
51. Mr Burke stated that controls in place since 1991 prohibited the use of protein derived from specified bovine offals in fertiliser. The

BSE Inquiry report stated that only a little agricultural fertilizer (less than 0.05%) contained a minimal amount of meat and bone meal. The TSE contamination of raw materials, historically used to produce fertiliser used for non-agricultural purposes was likely to be extremely low, as these fertilisers generally contained bone meal rather than meat and bone meal. It was noted that since 1996, MMBM was prohibited for use on agricultural land but not domestic gardens, and that since 1998, fertilisers used on non-agricultural land must have been derived by pressure rendering, thus substantially reducing the amount of infectivity, if present. The committee concluded that the risk of exposure to BSE infectivity from this route was very low and should not be of concern.

52. Mr Alcock noted that in the RoI, SRM was being transported in trucks, often with a simple tarpaulin cover and asked about the potential risk to humans from water splashing from trucks carrying SRM.
53. The committee agreed that this should not happen as SRM should be transported in leak proof containers. Mr Burke added that the EU regulations state that SRM must be transported in a covered leak-proof container, the material stained with a blue dye and the container clearly marked as 'category 1, for disposal only'. The committee suggested that if Mr Alcock believed SRM to be illegally transported then it should be reported to the relevant enforcement body in the RoI.
54. Mr Harry Marquess (Association of Northern Ireland Master Butchers) asked whether there was a possibility of the current vertebral column (VC) controls on over 24 month cattle being lifted by the end of the year.
55. Mr Burke explained that, before the lifting of the beef export ban, the UK had been given a special derogation to classify VC as SRM in cattle aged over 30 months, rather than over 12 months. On the basis of an European Food Safety Authority (EFSA) risk assessment, the EU increased the age limit from 12 to 24 months at the start of 2006. EU SRM controls were harmonised as a consequence of the lifting of the UK beef export ban in May 2006. EFSA is conducting a further risk assessment to determine whether the limit should be increased from 24 months. It was estimated that the EU may make a decision, based on this risk assessment, in early 2007.

56. Mr Marquess also asked when VC, from cattle aged over 30 months, could be boned out at butchers shops. Dr Gleadle explained that currently VC SRM from animals aged between 24 and 30 months could be boned out in authorised butchers shops however cattle aged over 30 months must be boned out in an additionally licensed cutting plant. There were currently no plans to change this.

ITEM 9 – EVALUATION CRITERIA FOR ANTE MORTEM DIAGNOSTIC TESTS FOR SUBCLINICAL vCJD (SEAC 94/3)

57. The Chair explained that the UK blood services and DH requested SEAC's advice on the scientific criteria by which ante mortem diagnostic tests for subclinical vCJD could be validated. A position statement would be produced based on the committee's consideration.
58. Dr John Stephenson (DH) presented an overview of DH research related to the development and evaluation of ante mortem tests for vCJD, prototype tests developed by commercial companies and the work of DH advisory committees that had considered issues related to diagnostic tests for vCJD. The available information on prototype tests was limited for reasons of commercial sensitivity, however most, if not all, appear to be based on the detection of PrP^{Sc}. DH had set up a CJD Tissue Management Group to oversee the collection and allocation of human tissues with which to evaluate tests. However a new group was being convened with a wider remit that included the allocation of blood samples and oversight of the vCJD tissue resource centre at the National Institute of Biological Standards and Controls (NIBSC). A Subgroup of the Committee of Microbiological Safety of Blood Tissues and Organs had provided advice on the preparative work required, should a screening test for subclinical vCJD become available. The Subgroup concluded that, unless a test was developed with very high specificity, large numbers of false positive results would be obtained leading to an unnecessary shortage of blood, therefore a reliable confirmatory test was required. Establishment of a panel of blood samples from cohorts of UK and USA blood donors to evaluate diagnostic tests was also recommended. The HPA Expert Advisory Group on a Testing Strategy for NATA was considering the criteria for screening tests for tonsil samples. The UK blood services have also convened the Prion Assay Working Group to provide guidance on the suitability of diagnostic tests for use within the blood services. The ethical implications of screening tests for subclinical vCJD had been

considered by the HPA, together with the Nuffield Council for Bioethics and a report was due for release.

59. Dr Roger Eglin (National Blood Service) presented an overview of the performance requirements for screening tests for subclinical vCJD for use in the blood services. It was considered that a screening test must be CE marked²³ and meet an, as yet undefined, Common Technical Specification (CTS) for an Annex IIA assay, as specified in the In Vitro Diagnostic Medical Devices (IVD) Directive 98/79/EC. Initially a test should have a sensitivity of at least one infectious dose (ID)/mL and a specificity that gave an initial reactive result rate of below 0.3% and for a repeat reactive result rate of below 0.15%. A panel of blood samples is being prepared from 5 000 UK and 5 000 USA blood donors separated into plasma, red cells and white cells to assess the specificity of blood tests. It was envisaged that one or two other tests would be performed on reactive samples from a screening test to confirm the presence of PrP^{Sc}, with repeat positive results resulting in deferral of the blood donor. Reactive samples from the screening test could be confirmed by the secondary or tertiary test, as the tests would all use a different mechanism(s) to capture the analyte.
60. Dr Philip Minor (NIBSC) presented an overview of the samples available for use in evaluation of tests for subclinical vCJD. These include dilution series of brain and spleen from vCJD cases and classical scrapie infected sheep, blood spiked with brain or spleen from vCJD cases or healthy individuals and blood samples from classical scrapie infected and healthy sheep. It was proposed that large numbers of blood samples from classical scrapie endemic and classical scrapie free flocks, UK and non UK blood donors and importantly blood from vCJD cases be collected to assess and compare the performance of diagnostic tests. In addition, panels of blood collected from mice and sheep through the TSE incubation period, from individuals classified as 'at risk of vCJD for public health purposes' and from haemophiliacs would also be useful to assess the time in the incubation period when blood become infectious and detectable by tests.
61. Dr Minor noted that, at present, the performance of tests was not specified and they could be freely marketed. However, should diagnostic tests for subclinical vCJD be included in Annex IIA of the IVD Directive 98/79/EC, all such tests would have to comply with a CTS.

²³ CE (Conformité Européene) mark is a declaration by the manufacturer that a product meets all the necessary requirements of the relevant EU legislation.

62. Dr John Parry (HPA) provided an overview of the issues arising from the evaluation, validation and implementation of blood tests in relation to the human immunodeficiency virus.
63. Members agreed that it was very important that diagnostic tests for subclinical vCJD be included in Annex IIA of the IVD Directive 98/79/EC, to ensure proper evaluation against a CTS.
64. A member noted that all the diagnostic tests were based on the major assumption that PrP^{Sc} is a good marker of the infectious agent, however PrP^{Sc} does not always correlate with TSE infectivity. As a better marker has not been identified, PrP^{Sc} is currently the most appropriate marker, although this assumption should be reviewed in light of any data that may become available. It must be recognised that PrP^{Sc} levels are a non quantitative measure of infectivity. As the relationship between PrP^{Sc} and the infectious agent is unclear, tests that recognise different parts of the PrP^{Sc} molecule may produce conflicting results, possibly making it difficult to identify suitable confirmatory tests. Therefore, it would be very important in the evaluation of screening and confirmatory blood tests that blood from vCJD cases be tested, as blood from animal models or blood spiked with vCJD brain or spleen may not reflect the response from tests when applied to the detection of the vCJD agent in blood. Preliminary evaluation of the specificity and sensitivity of tests could be achieved by using spiked blood or blood from animal models, however final evaluation of tests must include blood from vCJD cases.
65. A member queried whether there was any evidence that PrP^{Sc} is in a different form in blood than in spleen or brain. Dr Minor responded that there were no such data, however some tests were able to detect both PrP^{Sc} in the brain and spleen, providing some assurance that the test may detect the form of PrP^{Sc} in blood. A member suggested that PrP^{Sc} may be in a more soluble form in blood compared with the form in spleen or brain, thus it was important to collect blood from preclinical and clinical vCJD patients for use in the assessment of the efficacy of blood tests and to assess the point in the incubation period when blood becomes infectious. Blood collected from individuals "at risk of vCJD for public health purposes" would provide a valuable source of blood from potentially preclinical vCJD cases. This issue was being considered by CGAG.
66. Members agreed that independent evaluation of tests using the same panels of blood was very important. Dr Eglin noted that the

blood services have a Kit Evaluation Group which independently evaluates test kits, using staff trained by the companies in the use of their products.

67. A member noted that two key considerations for the applicability of a blood test were the volume of material required and the reproducibility of a concentration step, should it be required. Dr Minor responded that tests vary in the volume of sample required and the requirement for sample concentration. However manufacturers recognise the difficulty a concentration step poses to the blood services.
68. It was noted that work with the vCJD agent requires a category 3 containment facility. Dr Eglin responded that, as for the blood born viruses, the screening is conducted on a largely negative population and can be derogated to category 2 laboratory conditions. However, further testing on reactive samples would be undertaken in a category 3 laboratory.
69. A member asked whether any of the prototype diagnostic tests had been assessed using blood from classical scrapie infected and healthy sheep. Dr Minor explained that some companies had obtained these samples and had been able to correctly identify blood from infected animals. It was important that the same panels of blood samples be sent to manufacturers to ensure a consistent approach. However, stocks of these samples may be insufficient to evaluate the number of diagnostic tests that may become available.
70. A member asked about the collection of blood from vCJD patients and whether there were sufficient samples available to evaluate tests. Dr Knight explained that relatively small amounts of blood had been collected and this had been fractionated into plasma, red cells and white cells. Dr Minor suggested there was insufficient blood from vCJD patients to conduct proper evaluations with the required number of replicate tests. A member suggested collection of larger volumes of ante mortem blood from vCJD cases. It was also suggested that blood collected at post mortem from vCJD cases would be a source of large quantities of blood. Dr Knight explained that not all vCJD cases underwent autopsy and many were performed up to two days after death when significant autolysis may have occurred. Furthermore, it is difficult to obtain large volumes of blood post mortem. It was suggested that blood from familial cases of CJD be collected. Members noted that the form of PrP^{Sc} may be different between familial CJD and vCJD and that, unlike vCJD, familial cases of CJD did not express PrP^{Sc}

systemically. Members suggested that a non-human primate model of vCJD could provide large volumes of blood.

71. The Chair considered it important that the volume of blood required to evaluate diagnostic tests be calculated and that a mechanism to acquire sufficient blood from vCJD patients was developed. Replicate tests to evaluate the efficacy of tests could be conducted using spiked blood samples and, or, blood from animal models. However it is very important that the final evaluation is conducted using blood from vCJD cases. Dr Stephenson noted that the CJD Tissue Management Group was established to ensure that tissue samples from vCJD cases were used appropriately. The Chair noted that a number of research organisations had collected blood from vCJD patients and these samples should be made available. A Group was required to calculate the quantities of blood required to evaluate tests, oversee the collection of samples, develop clear performance criteria that must be fulfilled by manufacturers before they receive these very valuable samples and to make decisions about the supply of these samples to manufacturers. Dr Stephenson responded that such a group was being convened at NIBSC. Members considered it important there is coordination of collection and supply of animal as well as human tissues.
72. The Chair suggested that risk assessments be conducted to examine the required sensitivity and specificity for blood tests and to examine scenarios of the effect of such tests on the blood supply and transmission of vCJD.
73. Members noted that use of screening tests was not restricted to the blood services and tests could be used for other purposes with less stringent performance criteria. Use of tests for other purposes may create a market that encourages commercial companies to develop improved tests.
74. A member asked when an evaluated test might be available. Dr Minor responded that a preliminary evaluation of tests could be started relatively soon, however it was difficult to predict when a fully evaluated and validated test may be implemented. Members recommended that the ethical issues must be resolved prior to the introduction of a blood test.
75. The Chair summarised the discussion, noting that:
 - Until diagnostic tests for subclinical vCJD are included in Annex IIA of the IVD Directive 98/79/EC and validated against a defined CTS, the CE mark cannot be relied upon to indicate

a test had been properly evaluated and validated. In the meantime, tests should be independently validated using blinded samples.

- Preliminary evaluation of the specificity and sensitivity of tests could be achieved using blood spiked with brain or spleen from vCJD cases or blood from animal models. However, it is very important that the final evaluation include testing of blood from vCJD cases.
- It is critical to collect sufficient quantities of appropriate tissues, to prepare panels of samples with which to evaluate and validate tests and to manage this material appropriately. Mechanisms need to be put in place to ensure these are readily available for testing potential products, but that guard against inappropriate use of a valuable resource.
- Risk assessments are required to establish the performance requirements of blood tests and to examine scenarios of the effect of introduction of such tests on the blood supply and transmission of vCJD.
- The ethical issues around ante mortem testing for subclinical vCJD need to be resolved prior to implementation of such tests.

ITEM 10 – ANY OTHER BUSINESS

76. There was no other business.

77. The Chair thanked all those who presented to the committee and taken part in discussions.