



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Minutes of the open session of the 90th meeting held on 24th November
2005

Roxburghe Hotel
38 Charlotte Square
Edinburgh
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- Members: Professor C. Higgins (Chair)
Mr. J. Bassett
Professor D. Brown
Dr. J. Chambers
Professor N. Hooper
Mr. P. Jinman (Deputy Chair)
Professor J. Manson
Ms. D. McCrea
Professor G. Medley
Professor J. Nicoll
Dr. P. Rudge
Professor M. Stanley
- Assessors: Mr. A. Harvey (FSA)
Mrs. E. Lawrence (DH)
Dr. P. Christie (SE)
Dr. A. Douglas (DARDNI)
Dr. M. Simmons (NAW)
- Technical Experts: Dr. P. Barrowman (Defra)
Dr. P. Bennett (DH)
Mr. P. Burke (Defra)
Miss. A. Conroy (FSA)
Dr. S. Dixon (FSA)
Professor N. Gill (HPA)
Dr. I. Hill (FSA)
Dr. D. Matthews (VLA)
Dr. J. Stephenson (DH)
Professor J. Wilesmith (Defra)
- SEAC Secretary: Miss K. Richards

Secretariat: Dr. T. Barlow
Dr. N. Ebenezer
Dr. P. Keep
Dr. V. Lund
Dr. C. Ravirajan

Also in attendance: Professor J. Ironside (National CJD Surveillance Unit) for item 4.

ITEM 1 – CHAIR’S INTRODUCTION

1. The Chair welcomed everyone to the 90th meeting of SEAC, the first in Scotland. The Chair explained that every year SEAC holds a meeting in one of the devolved administrations to make the committee’s work more accessible to the public. He thanked the Scottish Executive Health Department for hosting the meeting and a dinner for SEAC members the preceding evening, and Peter Christie and Margaret Tannahill for helping to organise this meeting.
2. The SEAC Secretary explained that open meetings allowed the public an opportunity to observe the committee at work and gain an insight into how an advisory committee provides independent scientific advice to Government. External experts involved in the issues that the committee will be considering are present and will be invited to the committee table. Government officials responsible for TSE policy may also be invited to contribute to discussions.
3. The committee will hold a reserved business session to allow discussion of unpublished scientific data on vCJD infectivity in blood, unpublished research in animal models examining human-to-human transmission of vCJD, and the correlation between abnormal prion protein concentrations and TSE infectivity. This is in accordance with the SEAC Code of Practice and a summary of these discussions will be posted on the SEAC web site.
4. Apologies for absence had been received from Ms. Diane McCrea and Professor Corinne Lasmezas.
5. Members were reminded that they are obliged to declare any commercial or other interests they may have in the agenda items. They were also reminded of the obligation to notify the Secretariat of any changes to the register of members’ interests as soon as they occur.
6. The next meeting will be held on Friday 24th February 2006 at the Royal Horticultural Halls and Conference Centre in Westminster, London.
7. The Secretary updated the committee on the following issues:
 - An EFSA opinion on rapid post-mortem TSE tests for small ruminants was published on 28th September.

- The report of the June 2005 mission of the Commission's Food and Veterinary Office to Great Britain concerning protective measures against BSE has been published on the Commission's website. Satisfactory progress had been made in most areas.
 - The Secretariat had informed Sheep Subgroup members of a Defra consultation on a TSE breeding programme for rare breeds of sheep, and requested they respond to the Secretariat by 16th December 2005. SEAC members were requested to comment by the same date to enable a co-ordinated response to be submitted to Defra.
 - Defra is consulting on lifting the export ban and harmonising Specified Risk Material (SRM) controls applicable in the UK with those in other member states. Members were requested to respond individually to Defra by 4th January 2006.
 - The National CJD Surveillance Unit (NCJDSU) 2004 Annual Report was published on 7th November.
 - The SEAC Secretary will attend meetings of the MRC's New Therapies Scrutiny Group as an observer. This group is taking over the work of the CJD Therapy Advisory Group.
8. In future, to save time at meetings, a list of these issues for information would be tabled, together with relevant website addresses.
 9. The Chair welcomed Professor James Nicoll to his first SEAC meeting.
 10. The Chair explained that the agenda for the open session consisted of a number of short items rather than substantive items. This was because a considerable amount of SEAC's current work, in particular discussion of atypical scrapie and the nature of the vCJD epidemic, was under consideration by experts in the SEAC Sheep Subgroup and the SEAC Epidemiology Subgroup, respectively. Reports from these subgroups would be discussed at a future SEAC meeting.

ITEM 2 - APPROVAL OF MINUTES FROM SEAC 89 (SEAC 90/1) AND MATTERS ARISING

11. The minutes of the open session of the 22nd September 2005 meeting were agreed as a correct record, subject to the following amendments:
 - paragraph 7, eleventh bullet point, line 3, change “...in the blood of scrapie affected hamsters...” to “...in blood samples of scrapie affected hamsters...”
 - paragraph 24, line three, change “...and new TSEs...” to “...and of identifying new TSEs...”.
12. The Chair noted that, as had been agreed at SEAC 89, a letter from SEAC had been sent to the Department of Health (DH) in response to the consultation on draft regulations under the Human Tissue Act 2004.

ITEM 3 - CURRENT ISSUES

13. The Chair updated the committee on the following issues:
 - The SEAC Sheep Subgroup will meet on 24th January 2006 to consider scientific developments regarding atypical scrapie and whether these have any implications for the National Scrapie Plan (NSP) or for the EU TSE roadmap. It was envisaged that the Subgroup would report to SEAC 91.
 - A report¹ on the detection of abnormal prion in the mammary glands of five Italian farmed Sarda sheep with coincident clinical signs of natural scrapie and mastitis was considered. SEAC discussed an experimental study using transgenic mice of the effect of concurrent inflammatory disease and TSE infection on the tissue distribution of PrP^{Sc} and infectivity at SEAC 86 (Heikenwalder *et al.*²). This report was from the same group, extending their observations to non-transgenic animals. A member commented that Sarda sheep are prone to particular diseases and that the sheep in this study had a specific type of mastitis not seen in the UK. Members also noted that it was unclear whether the sheep had clinical or subclinical mastitis since the mastitis agent involved did not

¹ Ligios *et al.* (2005) PrP^{Sc} in mammary glands of sheep affected by scrapie and mastitis. *Nature Medicine* 11, 1137-1138.

² Heikenwalder *et al.* (2005) Chronic lymphocytic inflammation specifies the organ tropism of prions. *Science*. 307, 1107-10. Discussion at SEAC 86 (March 2005).

lead to a greatly increased cell count in milk and was therefore difficult to diagnose. The committee noted that, in this study, the level of abnormal prion detected in mammary glands was considerably lower than the level of PrP^{Sc} found in the brain. Members noted that there is some consumption of sheep milk and milk products in this country but that legislation precludes milk from animals with clinical mastitis entering the food chain. A member commented that this would not be effective in the case of sub-clinical disease.

Members agreed that this was an important study, demonstrating the presence of abnormal PrP^{Sc} in unusual sites in sheep with two concurrent diseases. They noted that this was a specific, abnormal physiological situation. Furthermore, natural scrapie is not known to pose a risk to human health. The committee agreed that it would be important to consider the results of further work in future and whether other secondary infections might alter PrP^{Sc} distribution in prion infected animals.

In response to a question about the relevance of this study to mastitis in cattle, the committee was reminded that cows' milk was different from sheep's milk as the cell count was generally lower, and that there was no evidence of prion protein appearing in cows' milk or of maternal transmission of BSE. Dr Danny Matthews (VLA) commented that in experimental studies PrP^{Sc} had not been detected in milk from mastitic cows. He informed the committee that researchers in Switzerland are developing methods to look for prion protein in milk, therefore it might be possible to re-examine VLA-archived samples for prion protein using these new methods when available.

A member commented that, in interpreting the results of the human tissue studies regarding the presence or absence of PrP^{Sc}, it would be important to consider whether tissue was inflamed or not.

- An EFSA opinion on classification of atypical TSE cases in small ruminants was published on 10th November. The opinion includes an operational definition of atypical scrapie in small ruminants and concludes that sub-categorisation of scrapie and atypical scrapie would be premature at present, as there are insufficient data to quantify the implications of the impact of atypical scrapie, as distinct from scrapie, on animal health. The Sheep Subgroup will consider this opinion and

SEAC members are invited to send comments to the Secretariat.

- On 7th November, BSE testing of older cattle replaced the Over Thirty Months (OTM) Rule. The main public health protection measure, removal of SRM, remains in place. To date, 40 red meat cutting plants have been licensed to remove SRM bovine vertebral column from OTM animals and 19 abattoirs in GB had been approved for slaughter of OTM cattle for human consumption.
- On 28th October, the SEAC Chair and the Chairs of other committees concerned with CJD, met with DH and Health Protection Agency (HPA) officials to discuss current and future CJD issues. The SEAC Chair raised five issues that were key for SEAC: (i) atypical scrapie and its potential implications for animal welfare, the NSP and human health; (ii) the risk of secondary vCJD infection via blood transfusion and surgery, (iii) the possibility of a secondary epidemic of vCJD arising from such secondary transmission; (iv) the prevalence of BSE infection in man and the likely size of the current vCJD epidemic; and (v) the true nature of the TSE infectious agent and its implications for the development of antemortem diagnostics. As a result of the meeting, David Pryer, Chair of the CJD Incidents Panel (CJDIP), had been invited to SEAC 90.
- On 31st October the FSA held a meeting to enable the new Chair of the FSA Board, Dame Deirdre Hutton, to meet the Chairs of all the FSA advisory committees. Peter Jinman, SEAC Deputy Chair, represented the committee.
- On 30th September, the SEAC Chair attended a workshop sponsored by the Royal Society and FSA. The aim of the workshop was to decide to what extent the approach of Government's independent advisory committees to risk assessment should be informed by the social sciences as well as the sciences. He presented a case study on SEAC's involvement in review of the OTM Rule, which was considered a good example of how risk assessment and management could be progressed by advisory committees and the Government.
- The Secretariat is running an exercise to recruit two new members to SEAC: one member with veterinary clinical expertise to replace Peter Jinman who comes to the end of his

second term of office in April 2006, and one member with veterinary molecular and biochemical expertise to replace Professor Ian McConnell who left the committee in August 2005. An advert has been published in the Veterinary Record and on the SEAC website. The Chair encouraged members to make these opportunities known to suitably qualified colleagues.

ITEM 4 – vCJD UPDATE

14. The Chair invited Professor James Ironside (NCJDSU) to update the committee on the number of cases of CJD in the UK and worldwide.
15. Professor Ironside informed the committee that the basic parameters of sporadic CJD (sCJD) remained unchanged. The clinical disease has a short duration of approximately 4 months with the mean age at onset of 66 (range of 15-94) and mean age of death of 67 (range of 20-95). There is no significant gender difference in sCJD incidence. Between May 1990 and August 2005, 788 cases of sCJD had been identified with a mean age at death of 66 (range 20-95) years. The number of deaths had increased steadily from almost 30 cases in 1990 to over 70 cases in 2003. In 2004 this had fallen to 50 cases and up to September 2005 just over 30 cases were reported. The apparent increase in cases to 2003 was considered to be a result of better detection of cases and this phenomenon was observed in other countries. However, the figures fluctuate and the increase that was seen in 2003 had not been sustained. The genotype distribution of sCJD cases was 65% MM, 17% MV and 18% VV at codon 129 of the prion protein gene.
16. The total number of definite and probable vCJD cases in the UK was 158, of which 7 cases were still alive. No significant gender difference had been observed in vCJD cases. All 134 of the UK cases that had been genotyped were MM at codon 129 of the PrP gene. Elsewhere in the world, 27 vCJD cases have been reported: 15 in France, 3 in the Republic of Ireland, 2 in the USA and single cases in Italy, Canada, Saudi Arabia, Japan, Netherlands, Spain and Portugal. For 1 Irish case, the Japanese, Canadian and both USA cases, infection could be attributed to infection in the UK. The clinical, pathological and prion protein codon 129 genotype of all these cases is similar to that of the UK cases.
17. The age distribution of vCJD had not altered over the course of the UK epidemic, with the mean age of death of 30 (range 14-74)

years and only a single case over 70 years. The stable age distribution may be explained by a combination of age-related exposure and age-related susceptibility to BSE. The mean age at death of the 13 French vCJD cases who have died is 38 years (median 36), age range 20-58 years, with a mean age at onset in the 15 French cases of 37 years (median 35), age range 18-57 years and a median duration of illness of 15 months (range 8-24 months). French cases were also of the MM genotype. This may be due to a later time of exposure to high-risk BSE infected food, but it was difficult to draw definitive conclusions as the number of cases is relatively small and not statistically significant.

18. Figures on the UK incidence of deaths from vCJD indicated the epidemic was in decline with a peak of 28 deaths in 2000. UK incidence of onsets of vCJD peaked in 1999 with 29 cases, declining to 5 cases in 2003, but rising to 9 cases in 2004. This increase might be an anomaly as the numbers are small, but this apparent upwards trend would continue to be watched very carefully. The 2004 cases of onset of vCJD are similar to previous cases in terms of genotype, age of onset and clinical symptoms.
19. Since only about two thirds of vCJD cases have been confirmed by neuropathological examination, a member asked about the reliability of the clinical diagnostic criteria for the remaining vCJD cases. Professor Ironside explained that clinical diagnosis had been extensively validated by comparisons with vCJD cases examined by neuropathological confirmation. In addition, magnetic resonance imaging (MRI) scans of the brain were also undertaken and in some cases tonsil biopsy was conducted. A higher autopsy rate that would allow neuropathological examination would be preferable. A member asked about the ratio of medico-legal autopsies to hospital-consent autopsies in vCJD cases and was informed that although variable, they were roughly equal in number.
20. Professor Ironside presented data on biochemical typing of the prion protein by proteinase K followed by Western blot. The two main patterns in sCJD and vCJD cases; type 1 and 2, differ in the molecular weight of the non-glycosylated protein band. Type 2 cases could be further divided, depending on the relative intensities of the glycosylated bands, into types 2A and 2B. Type 2B is normally associated with vCJD but not with sCJD.
21. Professor Ironside explained that it has been suggested that biochemical typing could be used as a surrogate for TSE strain typing. However, recent biochemical typing studies of sCJD cases

had found more than one biochemical type of prion protein to be present in tissues from each individual, although one type usually predominates.

22. Similar studies on samples from vCJD cases had shown that all cases had more than one biochemical type. Thus, both type 1 and type 2 could be detected in a wide range of brain regions as well as the tonsil of vCJD cases, although smaller amounts of type 1 compared with type 2 prion protein were present. Minor amounts of type 1 prion protein were also found in the brain of cattle infected with BSE and in the brain of mice infected with vCJD, alongside the predominant type 2 form. Thus, type 1 prion protein is a minor component of the prion protein associated with vCJD in relation to the type 2 form. However, the ratio of the amount of the two forms remained the same, suggesting it is conserved when the agent is transmitted across species barriers. These findings suggest that the relationship between the properties of abnormal prion protein in biochemical tests and agent strain was more complex than previously thought.
23. A member suggested that a dynamic equilibrium between prion protein conformations of different energy states might be expected to exist, with a single low energy state predominating. It was noted that such an equilibrium might not be achieved in a biological system, and two folding forms of a protein could easily co-exist and would be influenced by factors such as pH, metal ion concentrations and importantly activation energies between protein folding states.
24. In response to questions about the experimental method, Professor Ironside indicated that the method had been standardised as far as possible to ensure that results were not generated as artefacts of the method. If other antibodies that recognised different epitopes were used it was possible that different banding patterns would be observed. Experiments that included chelating agent to remove metal ions had no effect on the types of prion protein found. Members noted that proteinase K digestion and Western blotting was a relatively crude method of analysis of prion protein conformation. Conformation dependent immunoassay may be a more sensitive method for this type of analysis.
25. In conclusion, the committee considered these important data, showing that current biochemical tests may not be sufficient to properly define strain type. This is due to limitations in our ability to experimentally distinguish different folding forms of a protein.

Importantly, the biochemical form(s) of PrP detected following infection appear to reflect both the infecting agent and the host PrP protein and may not be sufficient to define strain types.

26. The Chair thanked Professor Ironside for his presentation.

ITEM 5 – SEAC EPIDEMIOLOGY SUBGROUP UPDATE (SEAC 90/8)

27. The Chair explained that SEAC had tasked the SEAC Epidemiology Subgroup with considering the nature and future profile of the vCJD epidemic, taking into account new research and the likelihood of a self-sustaining epidemic arising.

28. Professor Graham Medley (Chair of SEAC Epidemiology Subgroup) introduced a position statement based on the SEAC Epidemiology Subgroup's discussions at meetings on 11th May and 13th September 2005. Discussions had focused on three main areas: (i) the prevalence, age and genotype distribution of vCJD infection, (ii) options for gathering further data to inform assessment of the epidemic, and (iii) the risk of a self-sustaining epidemic.

29. The Subgroup had noted that data on the prevalence of infection was presently limited to two sources, the vCJD case data and the retrospective analysis of appendix and tonsil tissues. In the absence of further direct data, modelling studies could be used to make inferences about the prevalence of infection in particular age groups or genotypes. However, precise conclusions about the future incidence of cases and prevalence of infectiousness could only be drawn from better estimates of prevalence, and age and genotype distribution of infection, from population studies. These were considered unfortunate gaps in our knowledge.

30. Age and genotype are perhaps the most important variables in understanding and informing management of the epidemic and the risks of onward infection. In terms of age-related infections, the Subgroup concluded there was good evidence that there is a peak in the susceptibility to vCJD at around 10-20 years of age. Age-related susceptibility on its own could explain the stable age distribution of vCJD cases, although a possible contribution from an age-related incubation period cannot be excluded. Estimates on the relative prevalence of infection in the population by age can be made, but it is not possible to estimate absolute prevalence of infection since the absolute prevalence of subclinical carriers is unknown.

31. The Subgroup had considered a variety of additional studies that could ascertain infection prevalence. A table was included in the statement that outlined options for such studies. It was recognised that no single approach was able to provide all possible data on the whole population. Consequently, a range of different data sources is required, in addition to diagnosis of clinical cases.
32. The Subgroup had concluded that they could not exclude the possibility that a self-sustaining, secondary epidemic of vCJD may be occurring. Blood transfusion and surgery appear to be the most likely routes of secondary transmission to sustain such an epidemic. However, direct determination of the prevalence of infection is the only way to ascertain whether a self-sustaining epidemic is occurring and its extent.
33. The Chair thanked the Subgroup for producing a very thoughtful and well written statement. The committee was asked to comment on the statement and decide how its conclusions could be taken forward.
34. Members suggested that the committee strongly support the recommendation made in paragraph 16 of the statement - that serious consideration be given to PrP^{Sc} testing of samples collected from autopsies since it was vital to determine infection prevalence. Retention of autopsy samples was also important to enable future studies, should improved analytical techniques be developed. The committee agreed that further detailed consideration of how such a programme could be put into practice was needed. Consideration of this issue would require input from legal and ethical experts and pathologists.
35. A member asked whether the Subgroup had considered how an emerging secondary epidemic might be recognised. It was explained that epidemiological reviews of vCJD cases, which were constantly being undertaken at the NCJDSU, might identify cases of potential secondary transmission. There has been one case of clinical vCJD with significant association to blood transfusion. No other case with clear epidemiological evidence that shows they arose from routes other than dietary exposure to BSE have been identified, although it cannot be excluded that some may have arisen from secondary transmission.
36. Members asked about the potential risks of secondary transmission via dentistry, and the possibility of using tissue removed during dental procedures for prevalence studies. It was noted that the current risk assessment of this route suggests that

there are a large number of dental procedures but the risks of transmission may be very low. It was considered that the very small amount of material, and the possibly very low levels of PrP^{Sc} in tissue removed during dentistry, may preclude analysis of this tissue in prevalence studies. Dr Peter Bennett (DH) explained that the existing DH risk assessment on vCJD transmission via dentistry is currently under revision in light of recent published evidence of poor decontamination practice in dentistry and ongoing studies of the potential infectivity of tissues that might be operated upon during major dental procedures. It was anticipated that this assessment would be presented at SEAC 91.

37. Members suggested that, with respect to paragraph 20, which stated maternal transmission of vCJD is likely to be inefficient, it may not be possible to make predictions about the efficiency of maternal transmission of vCJD. This was because of the lack of direct evidence. It was noted that maternal transmission of scrapie, could, under certain circumstances, be relatively efficient.

38. In summary, the committee:

- welcomed and endorsed the statement.
- agreed that a short statement would be produced by SEAC to highlight the urgent need for studies to ascertain the prevalence of vCJD infection in the UK population.
- agreed that further consideration on how the prevalence of vCJD infection might be best ascertained was very important, and should be followed up immediately by the SEAC Chair, the SEAC Epidemiology Subgroup Chair, and the Secretariat.

ITEM 6 – BARB CASE CLUSTERS

39. Professor John Wilesmith (Defra) updated the committee on the BSE cases born after the 1996 reinforced mammalian meat and bone meal ban in the UK (BARB cases). Around 116 BARB cases had been identified in Great Britain up to 22 November 2005, mostly through active surveillance. BARB cases had decreased in successive birth cohorts, from 44 in the 1996/1997 cohort to none to date in the 2000/2001 cohort. However, 3 BARB cases had been identified in the 2001/2002 cohort. Backcalculation of the prevalence of BARB cases indicated a drop from 130 infected animals per million (95% confidence interval 90-190) in the 1996/1997 cohort to 30 infected animals per million (95% confidence interval 10-60) in the 1999/2000 cohort. A shift in the geographical distribution of BSE cases, from the concentration of pre-1996 BSE cases in Eastern England to a more uniform

distribution of BARB cases, had occurred. However, it appeared that certain post-1996 cohorts had a higher exposure to BSE in certain areas for limited periods. Several clusters of BARB cases within herds had been identified (5 pairs, 2 triplets and 1 quadruplet).

40. A triplet of BARB cases in South West Wales had been investigated in detail. The triplet comprised 2 cases born in September and October 2001 and a third in May 2002. The animals born in 2001 were reared outdoors from the spring of 2002 but the animal born in 2002 had been reared indoors. Further investigation of feeding practices revealed that a new feed bin for the adult dairy herd had been installed in September 1998. In July 2002 the feed bin was emptied, but not cleaned, and relocated. All 3 BARB cases received feed from the relocated bin. This finding suggested the hypothesis that the feed bin installed in September 1998 was filled initially with contaminated feed, that remnants of this feed fell to the bottom of the bin during its relocation, and thus young animals in the 2001/2002 birth cohort were exposed to feedstuffs produced in 1998. No adult cattle had been infected because of the reduced susceptibility to BSE with increasing age.
41. Further investigation of multiple case herds had found no association of BARB clusters with the closure of feed mills.
42. Professor Wilesmith concluded that there is evidence of a decline in risk of infection for successive birth cohorts of cattle. The BARB epidemic is unlikely to be sustained by animals born after 31 July 2000. Feed bins could represent a continued source of occasional infection and advice to farmers is being formulated to reduce this risk. There is no evidence for an indigenous source of infection for the BARB cases.
43. Members considered it encouraging that no other factor, apart from feed contamination, had been identified as a possible cause of BARB cases to date. Members commented that this study suggests that only a small amount of contaminated feed may be required for infection and that BSE infectivity can survive in the environment for several years. Professor Wilesmith agreed and noted that infection caused by small doses of infectious material was consistent with other studies, and it would appear there is little dilution of infectivity, if present, in the rendering system. Additionally it appeared that the infectious agent had survived for 4 years in the feed bin.
44. The Chair thanked Professor Wilesmith for his presentation.

ITEM 7 – SLATE PAPER (SEAC 90/3)

45. SEAC considered a recent paper on molecular evolution of the sheep prion protein gene (PRNP) by Jon Slate³. The study investigated the evolutionary selection pressures acting on ruminant PRNP using a theoretical molecular evolution analyses of ruminant PRNP sequence data. On the basis of these analyses, the author concluded that PRNP in sheep had evolved by balancing selection rather than positive selection, to maintain variation in PRNP and include genotypes relatively susceptible to scrapie. This was in contrast to the aim of the NSP which is to selectively breed for genotypes relatively resistant to scrapie.
46. The Chair explained that, due to the specialist nature of the molecular evolution approach, the paper had been sent to two independent experts. Written reports from these reviewers had been provided to SEAC members. The experts had been asked to review the paper, comment on the methodology used, and on the implications for the NSP. Members noted that the referees had questioned the interpretation of the results of the analysis. One member agreed that the methodology employed in the Slate paper was appropriate, but that the interpretations were open to question.
47. The committee noted it had always considered it possible that a particular group of sheep could emerge, which were resistant to classical scrapie but susceptible to a change in the scrapie agent, leading to a different but susceptible population.
48. A member noted that the value of a SEAC recommendation to set up a semen archive to preserve genetic diversity had been borne out, and that the paper highlighted the importance of investigating any association between certain types of ram and production characteristics as recommended by SEAC. Defra has initiated studies to address both of these recommendations. Members noted that if desirable characteristics of sheep were lost by implementation of the NSP, consideration of the relative importance of these characteristics, and of mechanisms to reintroduce these characteristics, would be needed. The impact that the removal of scrapie-susceptible animals might have on rare breeds of sheep had been highlighted in the recent Defra

³ Slate (2005) Molecular evolution of the sheep prion protein gene. Proc. R. Soc. B. 272, 2337-2344.

consultation on a TSE breeding programme for rare breeds of sheep⁴.

49. It was concluded that the paper did not raise any new issues that had not already been considered. Further and more detailed consideration of these issues would be raised at the forthcoming SEAC sheep subgroup meeting. The Chair thanked the referees for their helpful comments.

ITEM 8 – HORIZON SCANNING

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

DH

51. Mrs Eileen Lawrence (DH) explained that the key priorities for DH were to prevent primary vCJD infections from animal sources, to minimise the risk of secondary infections by medical interventions, and to provide appropriate care and support to CJD patients and their families. With the decline in the number of BSE-infected cattle, and the introduction of key control measures, the focus was on minimising the risk of person to person transmission. DH would like the SEAC Epidemiology Subgroup to keep under review emerging research that might impact on this issue, and in particular any information from the CJDIP on specific cases of potential infection.
52. The meeting of DH and HPA officials with the Chairs of advisory committees, including SEAC, with an interest in TSEs had been very useful for sharing information and horizon scanning and these meetings would continue. One important issue arising from the recent meeting was the need to capture information in a systematic way on individuals identified as being at a greater risk of vCJD than the general population. DH had asked the HPA to develop proposals for a database to do this. Another issue raised at the meeting was the possibility of TSE testing of tissue collected at autopsy. It was suggested that an expert group of SEAC be convened to consider the ethical, practical and regulatory issues related to post-mortem testing.

⁴ Defra consultation on a TSE breeding programme for rare breeds of sheep. <http://defraweb/corporate/consult/tseprog-raisesheep/index.htm>

53. A further notification exercise concerning blood donors had begun in November 2005. This involved about 50 people who had received blood from a small group of donors identified previously as being at higher risk of vCJD than the general population. This notification exercise also helped reinforce the importance of preclinical vCJD diagnostic screening tests. Development of a preclinical diagnostic screening test remains one of the key priorities for the DH. In the future SEAC would be asked to assess the appropriateness of animal models to validate such diagnostic tests.
54. SEAC advice will also be sought on a number of risk assessments. These would include dentistry, the potential risk to highly transfused individuals who may have had greater exposure from vCJD infected donors, and medical devices derived from non-UK sourced bovine materials. The Medicines and Healthcare Products Regulatory Agency (MHRA) is in the process of negotiating the revision of European standard control measures to reduce TSE-related risks from medical devices that incorporate animal material. The MHRA, through DH, will ask SEAC for advice to inform its negotiations.
55. Members considered that the dentistry risk assessment should also be seen by the National Institute for Clinical Excellence (NICE) committee that is currently looking at transmission risks from surgical instruments. It was agreed that it would be important to set up an expert group to examine the ethical, practical and regulatory issues related to post-mortem testing. Involvement of the Human Tissue Authority in such discussions would be helpful. As similar issues had been raised on the retention of animal tissues for further analysis it was suggested that DH and Defra coordinate efforts on this issue.

FSA

56. Mr Alan Harvey (FSA) noted that there were a number of cross cutting issues for FSA, DH and Defra, such as the development of an ante-mortem TSE test. From an FSA perspective, it was notable that there had been a decline in the incidence of BSE from 34 000 cases in 1992 to 90 clinical cases in 2004, and that the government had a target to eradicate BSE by 2010. The incidence of BARB cases may be a challenge to the eradication programme but the control measures put in place appear to be working. Therefore, although there is some uncertainty about the possibility of BSE in the national sheep flock, TSEs are no longer a major research priority for the FSA and funds for TSE research were

becoming more limited. Nevertheless, FSA would continue to seek and value SEAC advice on emerging research findings and assessment of the risks of changes to, or relaxation of, existing control measures. FSA's 5-year plan to develop an ante-mortem diagnostic test remains and FSA is organising a workshop, in December 2005, to discuss progress in the development of the non-invasive diagnostic test.

57. Dr Danny Matthews (VLA) considered it vital that relevant TSE materials be produced and stored to validate any preclinical TSE diagnostic tests that become available in the future. The committee agreed that this was very important and that this issue should be considered at the FSA workshop on the development of the TSE diagnostic tests. Dr John Stephenson (DH) noted that DH has set up a CJD Resource Centre at the National Institute of Biological Standards and Controls specifically to provide validated materials for the assessment of CJD diagnostic tests. A tissue management group has been set up to allow diagnostics companies to apply for access to tissues for test evaluation. Companies developing tests had applied for access to this material: some of these tests look promising and not all depend on proteinase K digestion.

Defra

58. Mr Patrick Burke (Defra) explained that Defra's forward look is largely driven by the EU TSE Road Map's seven⁵ strategic policy goals. The EU Commission is in the process of prioritising these policy goals and will complete this process by the first quarter of 2006. SEAC will be consulted on the appropriateness of the EU proposals. As Defra's main aim is to protect consumers by eradicating TSEs, any changes to the EU proposals should be supported by scientific evidence and robust risk assessment. Since TSE surveillance, SRM controls and feed controls are linked, any changes to these needed to be considered together. Epidemiological data would be used to assess the effectiveness of changes to control policies.
59. Specific issues for Defra include the beef export ban, which Defra hope will be lifted in early 2006, the end of the OTM Scheme in early 2006, and the Older Cattle Disposal Scheme (OCDS) for cattle born before August 1996. BSE will be monitored continuously and BSE surveillance will focus on post-1996 cohorts. Defra will be responding to the recommendations of Professor

⁵ Specified risk materials, feed ban, surveillance, country classifications, small ruminant culling policy, bovine cohort culling, and UK exports.

Hill's report on BARB cases. SEAC will also be consulted on any new plausible hypotheses on the origin of BARB cases. An EU deer surveillance programme on wild and farmed deer will start in late 2006. It was likely that funding for TSE-related research would become more focused.

60. One member asked whether there would be any increase in the number of fallen stock animals tested after the change in the regulations on casualty animals. It was explained that EU member states are obliged to test all fallen cattle and all emergency slaughtered cattle aged over 24 months. Defra anticipates that the changes to the emergency slaughter regulation (1 January 2006) and the end of OTM Scheme will move more animals from the emergency slaughter stream into the fallen stock testing stream, but the overall level of surveillance will be unchanged.
61. The Chair thanked the assessors for their presentations.

ITEM 9 - PUBLIC QUESTION AND ANSWER SESSION

62. 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 take risk management or policy decisions on behalf of Government.
63. Mr Graham Steel, co-founder of the CJD Alliance, asked two questions, (i) in relation to the recently published paper by Alvarez *et al.*⁶ on the potential of (FLAIR) MRI for detecting CJD before the onset of clinical symptoms - does the committee acknowledge this development of early diagnosis may pave the way when considering issues such as putative treatments? (ii) when considering environmental issues, will SEAC be seeking to establish the outcome of the FatePride study, which is scheduled to conclude on 1st January 2006?
64. A member agreed that it would be very important to be able to diagnose vCJD early, so that if and when there was an effective treatment it could be used as early as possible. It was explained that some clinical cases of CJD show abnormalities on MRI scans and MRI is useful in diagnosing vCJD. Alvarez *et al.* report findings in an 80 year old woman who presented with a

⁶ Alvarez *et al.* (2005) Magnetic resonance imaging findings in pre-clinical Creutzfeldt-Jacob disease. *Intern. J. Neuroscience*, 115:1219-1225.

subarachnoid haemorrhage and abnormalities on MRI scan. Two years later she was diagnosed with sCJD and had a further scan that also showed abnormalities. The authors suggest that the abnormalities in the first scan were in fact early signs of sCJD. The member said that, in his opinion, the abnormalities seen in the earlier MRI scan were most likely due to the subarachnoid haemorrhage, and that it would be entirely speculative to suggest that they were due to subclinical CJD. He suggested that it was unlikely that MRI would be useful for early pre-clinical diagnosis of CJD as this technique has low sensitivity and specificity, even in clinical cases.

65. A member who was involved in the EU FatePride study explained that biochemists and geochemists were trying to determine the role of environmental factors (e.g. distribution of metals in the soil, presence of organophosphate pesticides) in the development of prion diseases such as BSE, scrapie and CJD. The study was likely to be extended until mid 2006 and when it was finished, he would report the findings to SEAC.
66. Dr Brian Matthews noted that the available information on the incidence of CJD in various countries, other than the UK, indicates that there is no obvious decline in the numbers of cases being reported. However, in the UK there seems to have been a steady decline in the number of suspected cases, and therefore of confirmed cases, for the past several years. He asked 3 questions: (i) What are the causes of the decline in the number of suspected cases reported in the UK over the past few years? (ii) What is the effect of this decline in reports of suspected cases on the certainty of the decline of the number of new cases of vCJD reported in the UK? (iii) What is the effect of this decline in reports of suspected cases on the certainty that new cases of iatrogenic transmission of CJD and/or vCJD could be identified?
67. Professor Ironside commented that the number of suspected cases of sCJD reported each year had varied since surveillance began, but numbers had appeared to decline in the past 2 years. However, this was unlikely to be due to significant numbers of cases being missed. As a way of checking to see if cases had been missed, NCJDSU had looked back at diagnosed cases of atypical dementia but had not identified any cases of CJD. The recent decrease in numbers of suspected cases reported was therefore probably due to improvements in clinical diagnostic criteria and the resultant improved quality of referrals. NCJDSU had very good links with clinicians and pathologists across the UK.

68. Professor Ironside commented that the NCJDSU was involved in the Transfusion Medicine Epidemiology Review study that had led to the identification of the two probable cases of vCJD transmission via blood transfusion and was also involved in the Progressive Intellectual and Neurodegenerative Disease study of neurological disorders in children. While it was impossible to ensure identification of all cases of vCJD, those that were identified were thoroughly investigated to see if they could have been caused by secondary transmission.
69. The Chair thanked the members of the public for asking these interesting questions.

ITEM 10 - AOB

70. There was no other business.