SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Minutes of the open session of the 91st meeting held on 24th February 2006

Royal Horticultural Halls and Conference Centre
Greycoat Street
Westminster
London
SW1P 2QD

Members:	Professor C. Higgins (Chair)	
	Mr. J. Bassett	
	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:	Dr. A. Gleadle	(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)
	Dr. S. Dixon	(FSA)
	Professor N. Gill	(HPA)
	Dr. I. Hill	(FSA)
	Dr. D. Matthews	(VLA)
	Dr. J. Stephenson	(DH)
SEAC Secretary:	Miss K. Richards	
Secretariat:	Dr. N. Ebenezer	
	Dr. P. Keep	

	Dr. C. Ravirajan
Also in attendance:	Mr. J. Tinkler (Medicines and Healthcare Products Regulatory Agency) for item 5. Mr. S. Dobra (DH) and Dr. M. Turner (UK Blood Services) for item 6.

ITEM 1 – CHAIR'S INTRODUCTION

1. The Chair welcomed everyone to the 91st meeting of SEAC.

2. The SEAC Secretary explained that open meetings allowed the public an opportunity to observe the committee at work and provide an insight into how an advisory committee provides independent scientific advice to Government. External experts involved in the issues that the committee will be considering would be invited to the committee table to take part in discussions. Government officials responsible for TSE policy may also be invited to contribute to discussions.

3. The committee will hold a reserved business session in the afternoon to allow discussion of unpublished scientific data on possible transmission of vCJD via dental procedures. This is in accordance with the SEAC Code of Practice. A summary of both the open and reserved business discussions will be posted on the SEAC website next week.

4. The Secretary explained that:

   - as agreed at the last meeting, a list of website addresses of recently published reports relevant to TSEs would be tabled at each meeting.
   - the 2005 SEAC Annual Report will be published on the website next week. The format of the report has been altered substantially and comments on the new format would be welcome.
   - she had attended the second meeting of the MRC's New Therapies Scrutiny Group as an observer. Updates on the developments on CJD therapies, including studies on a humanised therapeutic monoclonal antibody and pentosan polysulphate, were presented together with small molecule developments.
   - she had attended a networking meeting of the secretariats of EFSA and other European advisory committees and representatives of other Member States dealing with TSE issues. This network would continue and aims to establish good working relationships and communication channels in common areas of interest, foster collaborations, share information and avoid duplication of effort.
   - she is now the press officer for SEAC. Members were reminded to discuss all requests from the media as a member of SEAC with either the SEAC Secretary or Chair as outlined in the SEAC Code of Practice.

5. Apologies for absence had been sent from Professor David Brown and Dr Jackie Chambers.

6. Members were reminded that they are obliged to declare any commercial or other interests they may have at the start of the relevant 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.

7. The next meeting will be held on Friday 28th April 2006 at the Royal Horticultural Halls and Conference Centre in Westminster, London.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 90 (SEAC 91/1) AND MATTERS ARISING

8. The minutes of the open session of the 30th November 2005 meeting were agreed as a correct record, subject to the following amendment:

- paragraph 35, line 3, change *"There has been one case with significant association to blood transfusion."* to *"There has been one case of clinical vCJD with significant association to blood transfusion."*

ITEM 3 - CURRENT ISSUES

9. SEAC was informed about the following issues:

- The Chair had received a positive response from the Chief Medical Officer on the recommendations made in the SEAC Epidemiology Subgroup statement on the vCJD epidemic[1] and subsequent SEAC statement[2]. SEAC had recommended that better data on the prevalence, age and genotype distribution of vCJD infections, based on population studies, are required with some urgency. DH will convene an expert group to consider ethical, practical and legal issues to take the recommendations forward. The terms of reference and membership of the group are under consideration. The membership would include experts on epidemiology, pathology and the Human Tissue Act. Members were invited to contact the SEAC Secretary to forward suggestions for members of the group or if they wished to become involved in the group themselves.

[1] http://www.seac.gov.uk/statements/state260106subgroup.htm
[2] http://www.seac.gov.uk/statements/state260106.htm

- A consolidated SEAC response to the European Commission consultation on the Scientific Committee on Emerging and Newly Identified Health Risks report on the safety of human-derived products with regard to vCJD had been submitted. The overall view was that the report lacked clarity in a number of areas. A number of other UK committees with TSE related remits had also responded to the consultation.

- Professor Noel Gill (HPA) updated the committee on a third case of vCJD transmission associated with blood transfusion. This case was announced by the HPA on 9th February 2006. The recipient developed symptoms of vCJD about 8 years after receiving a non-leucodepleted blood transfusion from a donor, who had developed symptoms of vCJD about 20 months later. The genotype of the recipient has not been reported. A paper on the case is being prepared by the National Prion Clinic. Some, though not all, of a further 25 individuals who have received blood transfusions from donors who later developed vCJD would have received leucodepleted blood. SEAC was informed about the HPA notification exercise, follow up arrangements and further actions relating to these 25 individuals. The actions include contacting the General Practitioners (GPs) of these individuals to obtain clinical information, expert review of this information and the development of a research proposal for a longitudinal study on these individuals to include post mortem analysis. GPs had been given the option to refer these individuals to the National Prion Clinic, the National CJD Surveillance Unit or to a local neurologist who would be given information on how a TSE related evaluation might be conducted.

  Members agreed that this third case indicates that there is a relatively high risk of transmission of vCJD by blood transfusion. It was not known whether a tonsil biopsy had been conducted in this case. Such a biopsy was considered important to help ascertain whether tonsil biopsy could be used as a diagnostic test for clinical iatrogenic vCJD. It also was considered important to conduct autopsies on these remaining individuals on the event of their death to determine, amongst other things, the prevalence of infection in this group. Professor John Collinge (MRC – Prion Unit) considered it very important that these individuals had access to best practice care and counselling and be informed about clinical trials and the development of potential therapies. Members agreed that active approaches to obtaining tissues for testing and clinical

monitoring of these patients was important both to ensure best practice clinical care and for enhancing understanding of risks.

- Interviews had taken place for two new members for SEAC. The recommendations of the interview panel would be submitted to Ministers shortly.

ITEM 4 – BSE UPDATE

10. Mr Patrick Burke (Defra) presented epidemiological data on BSE cases in the GB cattle herd, and of cases in other countries, and summarised the surveillance undertaken in the UK. The GB BSE epidemic peaked in 1992 with over 36,000 cases confirmed. This has since been in steep decline with 203 cases confirmed in 2005 and only a few (n=18) confirmed cases so far in 2006. The average age of onset of clinical BSE has increased with time. The proportion of clinical suspect cases subsequently confirmed as BSE has declined, probably due to the reduction in number of BSE infected cattle in relation to the number with other diseases. The incidence of GB BSE cases born after the 1996 reinforced feed ban (BARB cases) was also in decline. To date, 124 GB BARB cases had been identified. Most of these were detected in casualty animals that had been subjected to emergency slaughter under the over thirty-month scheme. Data on the number of BARB cases by birth cohort showed a peak in 2003, a subsequent decline in 2004, but an increase in 2005. This increase could partially be attributed to the introduction of a cohort cull in March 2005, leading to earlier detection of BARB cases. In the absence of the cull, it is likely these cases would have only been detected in later years through active surveillance or as clinical cases. Epidemiological data on BSE worldwide showed a wide geographical distribution but an overall decline in the incidence of the disease.

11. Members asked about the increase in BARB cases in 2005. Mr Burke explained that introduction of the cohort cull in March 2005 allowed detection of positive cases at an earlier stage and could partially explain the increase observed. A member observed that the end of the Over Thirty Month Scheme and changes to emergency slaughter rules which both came into effect in early 2006 might have encouraged farmers to submit more older cattle for slaughter in later 2005, and this might also have contributed to the identification of more cases in 2005. In view of these variables, revised backcalculation estimates of prevalence in the BARB cohorts would be a more useful indicator than observed incidence. Dr Danny Matthews (VLA) noted that cattle born later were exposed to relatively low doses of infectivity compared with historic

exposures, and so would be expected to have relatively long incubation periods. Thus, it is likely that animals infected late in the epidemic have yet to be identified in relatively recent birth cohorts. The committee were satisfied that the increase in number of cases identified in 2005 was unlikely to reflect a real increase in the number of infected animals, but instead reflects changes in surveillance and other factors.

ITEM 5 – MEDICAL IMPLANTS CONTAINING BOVINE MATERIAL (SEAC 91/2)

12. The Chair explained that the Medicines and Healthcare products Regulatory Agency (MHRA) asked the committee to consider issues around potential BSE risks to humans from medical implants using bovine material from USA animals. SEAC was also asked to comment on a scheme developed by a British Standards Institution (BSI) committee to assess whether BSE risks associated with medical devices are minimised.

13. Mr Jeremy Tinkler (MHRA) summarised the regulations on medical devices containing animal materials in relation to TSE risks. The regulations are based on the principle that TSE risks must be eliminated or reduced as much as possible and residual risks must be acceptable when weighed against the benefits to patients. About 100 medical devices containing bovine material, which have tissue contact with the recipient, are available in Europe. They tend to be used to treat serious conditions and confer significant clinical benefit, such as heart valves for paediatric cases. At present there are no alternatives to the animal-derived materials used in these products.

14. Mr Tinkler explained that, although regulations are in place, no guidance exists on the acceptability of TSE risk control measures applied to animal material in medical devices. Careful sourcing of animal material tends to be the most practicable way of reducing the TSE risk. The lack of guidance has led to inconsistent interpretation of the regulations across Europe. This was recently highlighted by the certification by a Notified Body in one Member State of cardiovascular implants sourced from open cattle herds in the USA, recently reclassified as a Geographical BSE Risk (GBR) level III country. Certification was on the grounds of a lack of alternatives. However, the MHRA took the view that the TSE risk associated with these devices had not been minimised since it should be possible to source the material from another country or from closed herds. Therefore, the MHRA felt that it was inappropriate to market such products freely in Europe, and their

use should only be permitted on humanitarian grounds until the risk had been minimised.

15. The MHRA wished SEAC to advise upon 3 issues. First, can the TSE risk associated with medical implants utilising bovine material sourced from USA cattle be estimated, given that it might vary over time? Second, is there, or has there been a significant risk from the use of such products that might warrant action in addition to that already taken to limit use of the products? Third, can the standards that support the regulations be altered to facilitate more consistent decisions about the acceptability of products? To address this third issue, a BSI committee has proposed a scheme, outlined in SEAC paper 91/2, that consists of additional requirements for acceptability of TSE risks in relation to medical devices.

16. A member noted that there are a number of variables that influence the overall risks and benefits from medical devices containing bovine material. The presence of TSE agents in the implant is influenced by the type of tissue used. The site of implantation also affects TSE risk, implantation sites in contact with central nervous system (CNS) or the blood supply could raise transmission risks. In addition, the number of animals used per device would influence transmission risks. The potential benefit to patients is also influenced by the type of device, with the benefit ranging from life saving (cardiovascular implants) to enhancement of quality of life (orthopaedic footware). The range of availability of alternatives may also vary considerably depending on the device. Taking all these factors together there is likely to be a wide range in the risk : benefit ratio between medical devices and a 'one rule fits all' approach was unlikely to be meaningful. Mr Tinkler noted that sourcing, availability and safety measures for skin contact devices, such as orthopaedic footwear tended to be similar to those for consumer products, whereas more stringent safety and quality assurance measures were employed for medical implants (including collagen).

17. Members noted that the number of animals needed to source material for implants such as heart valves was likely to be small. It should be possible to reduce risks by sourcing these materials from closed herds or herds managed carefully to prevent the introduction of the BSE agent. Mr Tinkler agreed that it should be possible to use closed herds. Additionally, it was suggested that it may be possible to source materials from other species, such as pigs. Mr Tinkler responded that heart valves from pigs had been used in medical implants but porcine pericardium was too thin and

so bovine pericardium was used in most cases. Dr Matthews explained that the cost of using animals from closed herds for some devices may be prohibitively expensive, noting the material for many devices is sourced from animals slaughtered for human consumption. A member noted that if relatively few animals are required this should not be prohibitive for potentially life-saving devices.

18. Members asked about the age of the source cattle, noting that use of material from younger animals would markedly reduce risks. Mr Tinkler explained that animal age depended on the quality of the tissue required for the intended use. For example, 6 month old animals would be used to source pericardium or heart valves, however collagen would be obtained from older animals. Members suggested that age of animal be used as a risk reduction criterion. TSE testing of the source animal could also be used as a risk reduction measure, although such testing would not definitively prove an animal to be uninfected. Mr Tinkler noted that BSE testing had not been included as a requirement in the standard.

19. Members suggested that, because of the wide range of variables that influence the risk in relation to medical devices, it is more appropriate to conduct independent risk assessments on each device. The characteristics of the device, the tissue and source animal all influence the risk to varying extents.

20. Members considered that GBR status gives a very imprecise indication of BSE risk. In relative terms, the BSE risk was likely to be lower in a GBR I country compared with a GBR III country, but the difference in risk cannot be quantified. In terms of a more robust risk analysis, it is important to obtain a more reliable estimate of the prevalence of BSE in a country than simply GBR status, and have confidence in the quality of the surveillance data. Since all the necessary BSE surveillance data from the USA are not publicly available, it is not possible to accurately determine the prevalence of BSE in the USA. Dr Matthews noted that at the time the standard was developed, GBR status, while crude, was the only tool available to assess risk and that it reflected the uncertainties in the data available. In the future, the GBR categorisation would to be replaced by a simplified classification in line with an Office International des Epizooties (OIE) categorisation. He pointed out that such schemes took into account of exposure to the BSE agent from the UK or other countries and that they were developed in the context of uncertainty about the infectivity of particular tissues.

21. Dr Matthews noted that data are now available on the infectivity of a wide range of bovine tissues. In September 2005, the World Health Organisation had updated its assessment of the risk of TSE infectivity in tissues. These data, although incomplete, should increase confidence in the safety of particular tissues, particularly if the age of the source animal is also considered. As a result, less reliance need now be placed on the status of the country of origin. Members agreed, but noted that it would be important to assess the quality of the data on which assessments are based. As it seems highly likely that blood, at least from humans infected with vCJD, can be infectious, tissues and organs with a significant blood supply may also confer higher risk.

22. Members noted that some of the definitions used in the BSI scheme were poorly defined and non-quantitative. Furthermore, there was no quantitation of the maximum acceptable risk - it was not appropriate to consider that just because a risk has been minimised by available techniques, the absolute risk was acceptably low. In addition, the scheme appeared to attach similar importance to each risk reduction method and selectively apply them to each GBR status, which may be inappropriate.

23. In summary, the committee concluded that a risk assessment should be conducted on each device because of the large number of variables that influence associated TSE risks. Key factors which should be considered when assessing risks are:

    - the animal source. Use of material from closed herds or from herds that are managed carefully to prevent the introduction of the BSE agent.
    - use of material from young animals would markedly lower risk compared with older animals.
    - the geographical risk of BSE. When assessing the geographical risk of BSE, the GBR status of a country gives an imprecise indication of BSE risk. It would be better to use an estimated prevalence of BSE in a country based on data from a robust surveillance system.
    - the potential TSE infectivity of the source tissue(s) based on a careful assessment of the available data on tissue infectivity.
    - the site of implantation. Sites with contact with the blood supply or CNS may increase risk.
    - whether TSE testing is undertaken on the source animal(s).
    - the number of source animals used for each device.

ITEM 6 – METHODS TO EVALUATE THE EFFICACY OF PRION REDUCTION FILTERS (SEAC 91/3)

24. The Chair explained that the UK Blood Service (UKBS) had previously asked the committee's advice about the implementation of prion reduction filters as a blood safety measure. SEAC had recommended that UKBS commission an independent validation of the filters and produce an assessment of the potential effectiveness of the filters to reduce transmission risks. The UKBS Prion Reduction Group has asked for the committee's input into the methodologies used to validate the filters.

25. Dr Marc Turner (UKBS) explained that two companies were developing prion reduction filters designed to remove prions from the red blood cell concentrate (RBC) of leucodepleted blood, Pall Medical Corporation (Pall) and Pathogen Removal and Diagnostic Technology Incorporated (PRDT). Pall has a CE mark[3] for its filter and the PRDT filter is expected to have a CE mark in the near future. Following SEAC's recommendation, UKBS had initiated an independent evaluation of the filters with two strands. One strand would evaluate the quality and safety of the filtered blood product. This would involve clinical studies and take about 18 months to complete. The second strand would evaluate the efficacy of the filters in removing prion infectivity. Due to the lack of sufficient blood samples of defined vCJD infectivity, it would not be possible to validate the efficacy of the filters directly. Three studies to evaluate the filters were proposed:

    (i) Measurement of the efficacy of the filters in reducing the infectivity in human leucodepleted RBC spiked with hamster scrapie brain, either as crude brain homogenate, microsomal fractions or sonicated microsomal fractions by biochemical assays and hamster bioassay. These experiments would allow the filters to be assessed using the same methodology as the companies. In addition, this approach would enable any substantial reduction in infectivity to be measured. This is important since risk assessments suggest that a 3-4 $\log_{10}$ reduction in infectivity would be required to significantly reduce transmission risks.

    (ii) Measurement of the efficacy of the filters in reducing the infectivity in human leucodepleted RBC spiked with splenic homogenate of mouse-adapted BSE. This would assess the efficacy of the filters in reducing the infectivity of a TSE strain more closely related to the vCJD strain in a different species.

[3] A declaration by the manufacturer that a product meets all the necessary requirements of the relevant legislation.

Additionally, different forms of homogenate would be used. These experiments should provide an indication of the utility of the filters to reduce infectivity of more than one prion strain.

(iii) Assessment of the filters in reducing endogenous infectivity in blood, recognising that brain and spleen homogenates are unlikely to represent the true physico-chemical nature of vCJD infectivity in blood.

26. Dr Turner explained that proposals had been invited to undertake studies (i) and (ii). These studies might start in summer 2006 with results available from the end of 2007. UKBS requested SEAC's advice at this stage on the suitability of studies (i) and (ii), guidance on the necessity and the model(s) that should be used in study (iii) and any additional work that would be useful to undertake.

27. Members welcomed the UKBS approach, in particular:

- the number of multiple filtrations that would be undertaken in the spiking experiments noting that in the published study by Pall only one filtration had been conducted,
- the selection of the 2 strains of TSE agent, noting that one was the widely used hamster scrapie strain on which there is an abundant literature. The second would be a BSE strain, which was of more relevance to the human situation.
- the high infectivity titres to be used allowing the filters to be tested over a wide dynamic range.
- the use of three different spiking materials allowing the filters to be tested on different types of preparations.

28. Members considered it important that study (i) replicated the companies' studies as closely as possible. Dr Turner explained that Pall and PRDT would be invited to prepare detailed dossiers of their work and to present their work to UKBS and the organisation selected to carry out study (i).

29. A member asked why the filters would only be tested using leucodepleted RBC since it was possible that the filter might not operate equivalently on leucodepleted and non-leucodepleted blood. Dr Turner explained that the filters were to be used in addition to leucodepeletion. Members recommended that the filters be evaluated on both leucodepleted and non-leucodepleted blood, since if they worked well on non-leucodepleted blood it may be possible to remove the leucodepletion step.

30. Members noted that the specification did not demand that experiments be conducted to good laboratory practice (GLP). Dr Turner explained that although it was not possible to conduct the work at full GLP because of the nature of some of the materials and protocols, it would be carried out to the highest possible standards and in the sprit of GLP. Members suggested that UKBS ask for the studies to be conducted to GLP with specified exemptions.

31. Members considered it necessary to conduct studies using endogenous infectivity in blood as it was crucial to use a model that reflected as closely as possible the human situation. It was noted that such experiments are difficult to conduct because of the difficulty in testing low levels of infectivity over a small dynamic range. Cost and experimental practicalities would need to be considered when selecting the most appropriate model but in scientific terms it was noted that:

    - rodent models allow bioassays to be conducted on the filtered material in the absence of a species barrier. The relatively short incubation period of TSEs in rodents would be advantageous. In addition, rodents have been used extensively in TSE studies so their characteristics are relatively well understood. However, the small volumes of blood that can be collected may be problematic. For example, given the known infectivity in hamster blood of about 10 ID_{50}/ml, the blood from about 250 clinically infected hamsters would need to be collected for filtration and inoculation to measure a 4 $\log_{10}$ reduction in infectivity. In mice with mouse adapted vCJD, the infectivity in blood is about 20 ID_{50}/ml. Humanised mice may be a better rodent model more closely reflecting the human situation, but the infectivity level in blood of such mice is unknown and the incubation period in these animals varies widely.
    - Non-human primates are the model that most closely reflects the human situation and large amounts of blood could be obtained from each animal. However, experiments would take a long time to complete. In addition, the infectivity titre in the blood of non-human primates was unknown. Experiments were being undertaken to investigate the vCJD infectivity titre in the blood of non-human primates but results would not be available for several years. Non-human primates could not readily be used as bioassays. Although humanised

mice could be used for this purpose their utility as bioassays for primate blood would need to be assessed. Use of non-human primates reflects the human situation most closely but raises cost as well as having ethical implications.

- Sheep had also been used as a useful model to assess transmission via blood. Ovinised mice could be used as bioassays for sheep blood and their utility for this purpose is currently being assessed.
- Development of cell based assays to detect TSE infectivity should be encouraged.

32. Members asked whether it would be possible to use blood from patients with vCJD as a final test of the filters. Humanised mice could be used as bioassays to assess the reduction in infectivity. Such experiments could provide information on the infectivity in human blood. Dr Turner explained that small amounts of human blood from patients with vCJD were available but to test a filter a whole unit of blood (450 ml) would be needed. Dr Stephenson noted that there were ethical concerns around the collection of blood from patients with vCJD, and the use of non-human primates, but recommendations from SEAC would strengthen applications to do such work. Members suggested that blood from individuals considered 'at risk of vCJD' should be collected with ethical approval and patient consent.

33. A member suggested that, given the difficulties in detecting infectivity in filtered blood, it might be easier to analyse the material retained on the filter. In the future, it might be possible to test this material to assess infection in individuals and ascertain the prevalence of infection from studies of large number of individuals. Infectivity studies could be conducted on the material collected by the filters.

34. A member suggested that provided the safety and quality issues had been addressed, and the results of studies (i) and (ii) demonstrated the filters to be effective, it might be possible to start using the filters before the results of study (iii) were known. Dr Turner agreed and noted that the Committee on Microbiological Safety of Bone, Tissue and Organs would need to consider this issue. Members agreed that ascertaining the prevalence of vCJD infectivity in the populations was a critical factor in this consideration.

35. Dr Peter Bennett (DH) noted that in evaluating the effectiveness of filters to reduce transmission risks it was important to know the

starting infectivity in specific blood components. There is presently a wide range of scenarios of infectivity. For example, it has been thought that infectivity may reside mainly in leucocytes. More recently it has been suggested that infectivity may reside almost solely in plasma. These different scenarios have a direct impact on the assessment of the effectiveness of the filters. It is envisaged that infectivity in specific blood components would be discussed at a future SEAC meeting.

ITEM 7 – SEAC SHEEP SUBGROUP REPORT (SEAC 91/4)

36. The Chair explained that, as he had been Chair of the SEAC Sheep Subgroup and was reporting back on its behalf, Mr Jinman (Deputy SEAC Chair) would chair the discussion of this item. Mr Jinman explained that since the introduction of the BioRad ELISA rapid test for active surveillance in 2002, around 100 cases of what is called atypical scrapie have been detected in the UK. These samples were not scrapie-positive as defined by confirmatory tests for classical scrapie. The SEAC Sheep Subgroup met on January 24th 2006 to consider the latest research findings related to atypical scrapie with the following aims:

    - to give the best interpretation of the current data on atypical scrapie and of the potential risks for animal and human health.
    - to consider whether new data change the risk basis underpinning the National Scrapie Plan (NSP), flock control, or relevant sections of the TSE roadmap.
    - to consider what additional information is necessary in order to improve assessment of the risk for animal and human health.
    - to produce a statement for consideration at SEAC 91.

37. Mr Jinman explained that the committee were invited to comment on the statement. Professor Higgins explained that atypical scrapie had been identified as a result of surveillance for scrapie and BSE in sheep. The SEAC Sheep Subgroup comprising UK and European experts on atypical scrapie met to consider published and unpublished data. The key conclusions of the Subgroup were:

    - it is possible, using biochemical tests, to distinguish reliably between experimental BSE in sheep, atypical scrapie and classical scrapie;
    - there is currently no evidence of BSE in the UK sheep flock.

- atypical scrapie is experimentally transmissible to mice and sheep, retaining its biochemical characteristics post-transmission;
- atypical scrapie is found independently of classical scrapie in some sheep flocks and goat herds;
- atypical scrapie should be considered as a distinct TSE in small ruminants, and not simply a variant of classical scrapie;
- although there is no evidence that atypical scrapie can be transmitted to humans, this possibility cannot be excluded and there is, therefore a theoretical risk to human health.

38. Professor Higgins explained that data provided by Professor John Wilesmith (Defra) from a GB abattoir survey of sheep over 18 months old suggested that the prevalence of sheep infected with atypical scrapie is estimated to be around 82 000 sheep compared with around 50 000 sheep infected with classical scrapie. Therefore, atypical scrapie infections are at least as prevalent as classical scrapie in GB, and may be more prevalent. This also appears to be the situation in at least some other European countries. However, in the UK, only 3 clinical atypical scrapie cases have been confirmed compared with 165 clinical classical scrapie cases, in the cases tested from July 2004 to 2nd December 2005. Possible explanations for the low number of clinical atypical scrapie cases relative to classical scrapie cases, may be the later onset of clinical signs in atypical scrapie or a different, although overlapping, clinical phenotype such that clinical cases of atypical scrapie have not been reported as a potential TSE infection. It is very important to define the clinical phenotype of atypical scrapie.

39. Professor Higgins explained that there are clear differences in the genotype distribution of classical and atypical scrapie. For example, the ARR/ARR genotype is relatively resistant to classical scrapie but relatively susceptible to atypical scrapie. VRQ/VRQ animals are susceptible to classical scrapie but no natural atypical scrapie infection has yet been detected in sheep of such genotype. Atypical scrapie can be experimentally transmitted to sheep and ovinised mice. There is currently no evidence for natural transmission of atypical scrapie into other species, including man. However, transmission to humans is theoretically possible. Classical scrapie is widely distributed in tissues in sheep, however the tissue distribution of atypical scrapie is not known. Information on the tissue distribution of atypical scrapie infectivity would inform possible Specified Risk Material (SRM) controls.

40. Professor Higgins explained that the Subgroup considered it would be important to ascertain whether atypical scrapie has spread recently through the sheep flock or, like classical scrapie, has been present for many years. The limited data obtained over the last 4 years do not indicate an increase in prevalence of atypical scrapie, however it is important to establish whether prevalence is increasing with time. If atypical scrapie has been in the small ruminant population for a long period, it may considered a low risk to human health since human exposure would have occurred over a long time with no apparent effect.

41. The Subgroup recommended additional research be carried out in a number of areas with some urgency.

42. In summary, the Subgroup had concluded that current data are insufficient for a meaningful assessment of risk from atypical scrapie, and the Subgroup recommended that further research is urgently undertaken. The Subgroup also noted that the NSP had been designed to minimise the risk if BSE ever entered the national sheep flock. As sheep genotypes relatively resistant to classical scrapie and experimental BSE appear susceptible to atypical scrapie, the Subgroup urged that the NSP is kept under constant review as new data emerge. Mr Jinman thanked Professor Higgins and all those who had participated in the SEAC Sheep Subgroup meeting.

43. A member asked what information would be needed to advise on changes to the NSP. Professor Higgins noted that there were many areas concerning atypical scrapie where experiments were ongoing, nevertheless further information and clarification was still needed. The statement outlined research recommended by the Subgroup. The main issue is the risk to human health. If it emerges that there is no risk to human health, the issue would then become one of animal health and welfare. The Subgroup report recommended several critical areas of research. Importantly, experiments inoculating atypical scrapie isolates into humanised mice are already underway in France, and other studies in humanised mice are planned the UK. Although atypical scrapie is a clinical disease, the animal health and welfare aspects of the atypical cases are not yet known.

44. Members noted that the GB prevalence of atypical and classical scrapie infection were of the same order of magnitude, but that atypical scrapie appears to occur at low prevalence in flocks which would imply that a high number of flocks might be infected. Members were informed that there are approximately 16 million

sheep in the UK, spread over about 60 000 sheep holdings. Dr Matthews noted that data on classical scrapie cases detected by passive surveillance, and recalculation of the number of infected flocks using data from a second postal survey of flock holders, also suggested a large number of flock infected with classical scrapie at low prevalence.

45. It was noted that atypical scrapie has also been identified in other European countries, such as Portugal, where all scrapie cases found by active surveillance have been classified as atypical scrapie. It was unclear whether the surveillance systems employed by countries designated as scrapie-free, such as New Zealand, would identify atypical scrapie.

46. Members agreed that it was important to be able to clinically differentiate between atypical scrapie, classical scrapie and other neurological diseases. Thus, there is an urgent need to establish the clinical characteristics of atypical scrapie.

47. Members welcomed the progress made so far and agreed with the recommendations for research made. The committee endorsed the SEAC Sheep Subgroup position statement, subject to a minor alteration to page 3, to take account of updated figures for the prevalence of TSE cases in sheep that could be BSE. The final sentence in this section would be altered to read: *"The extensive surveillance undertaken enables the prevalence of BSE in sheep, if it ever entered the British sheep flock, to be estimated at 0.54% (upper 95% confidence limit) of the total TSE cases in sheep, based on samples tested up to 30th November 2005 (2483 cases from 556 flocks)*".

ITEM 8 – USE OF LIVESTOCK AND CROPS FROM DRAYTON FARM (SEAC 91/5)

48. The Chair explained that Defra and FSA had asked SEAC to review the arrangements for disposal of manure, crops and livestock from an experimental farm on which BSE research had been conducted.

49. Dr Danny Matthews (VLA) outlined the geography and usage of areas of the farm and the arrangements made for treatment and disposal of animal excreta and milk. It was noted that SEAC had previously advised that manure from orally-challenged animals should be incinerated for the first 28 days. Thereafter the excreta should be composted for a year and then could be used to fertilise arable lands. No new scientific information was available to refine

this assessment and the effect of such measures had not been experimentally tested. As prion protein concentrations in excreta are low, it would be difficult to analyse infectivity levels experimentally. The 28 day period was derived from the time taken for materials to pass through the digestive tract of ruminants.

50. Members asked whether composting would help to reduce the concentration of abnormal prion protein. Dr Matthews replied that there is evidence that some bacterial enzymes are capable of digesting prion protein although this may not completely remove TSE infectivity.

51. A member asked about the type of material transported to Drayton Farm from VLA Weybridge. Dr Matthews explained that manure from around 80 cattle orally challenged with BSE, 30 challenged intracerebrally with BSE and 40 BSE-infected sheep contributed to the waste at Drayton Farm. Most of this material had been composted for periods of 1 to 16 years at Weybridge.

52. A member asked whether mouse bioassays had been conducted on faeces from clinical BSE cases. Dr Matthews explained that mouse bioassays on faeces from animals at 32 months post-BSE inoculation (3 months before the onset of clinical signs) were negative. Additionally, gut tissue from naturally infected animals with clinical BSE was negative by mouse bioassay with very low levels of PrP^{Sc} detectable by immunohistochemistry.

53. A member asked about the possible persistence of TSE agents in the environment, following the failure of a scrapie control programme in Iceland being attributed to the persistence of scrapie agent in the environment. Dr Matthews responded that the interpretation of the Iceland study was controversial. However, VLA studies showed that scrapie infectivity could persist in pasture for at least 2 months following contamination with excreta from infected animals.

54. Members noted that the buildings that had housed experimentally infected animals had been cleaned and treated with 20 000 ppm sodium hypochlorite. Members agreed that there is a negligible risk of BSE transmission to healthy animals housed in these buildings and that these animals could be used for commercial slaughter or other purposes. It was noted that the present animal tracing system would identify the origin of all animals from the site.

55. Members noted that there is no evidence to suggest that crops grown on land which had received manure from healthy control

animals would present a TSE risk. Operating procedures prevent cross-contamination of manure from experimentally challenged and control animals.

56. Members considered that there is no evidence that crops grown on the land which received composted excreta from BSE-challenged animals pose a TSE risk to humans or animals. One member suggested that, as some of these animals are orally challenged with high doses of BSE-infected materials, and the distribution of infectivity in the digestive system is not completely understood, it might be premature to conclude that there is no infective agent in the manure. Furthermore, an unpublished study had indicated low level absorption of PrP from soil by tomato plants although it should be noted that this study had not been repeated. Details of this work would be sent to the SEAC Secretary. Dr Matthews explained that most of the manure from animals challenged with high doses of BSE had already been composted and used for coppicing. Members agreed that the risks from disposal of residual manure from experimental animals would be much less than historic risks of on farm contamination from naturally infected animals at the height of the BSE epidemic.

57. Members agreed that there is there is no evidence to suggest that there is a TSE risk to humans or animals from the unrestricted movement of healthy sheep grazed on the grassland to which manure from non-BSE cattle was applied. In addition, there is no evidence to suggest there is a TSE risk from moving wood chips, harvested from the willow coppices planted at Drayton, grown on land that received manure from BSE challenged animals that had been composted for 12 months.

ITEM 9 - AOB

58. The committee noted that a table on EU TSE research had been provided by Dr Peter Barrowman (Defra).

59. The Chair closed the open meeting by thanking those that had presented to the committee.