SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Minutes of the 100th meeting held on 25th April 2008

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

Members:	Professor C. Higgins (Chair)	
	Professor J. Collinge	
	Professor A. Ghani	
	Professor N. Hooper	
	Mr. P. Jinman (Deputy Chair)	
	Dr. R. Knight	
	Professor C. Lasmezas	
	Professor J. Manson	
	Professor G. Medley	
	Professor J. Nicoll	
	Dr. R. Salmon	
	Professor A. Williams	
Assessors:	Dr. P. Christie	(SG)
	Dr. A. Gleadle	(FSA)
	Dr. S. Hayes	(NAW)
	Mr. M. Noterman	(DH)
	Dr. A. Douglas	(AFBINI)
Technical Experts:	Dr. P. Bennett	(DH)
	Mr. P. Burke	(Defra)
	Professor N. Gill	(HPA)
	Dr. J. Hope	(VLA)
Secretary:	Dr. P. Grimley	
Secretariat:	Dr. T Barlow	
	Mr. B. Cole	
	Dr. D. Cutts	
	Dr. A. Patey	
	Dr. C. Ravirajan	
Also in attendance	Mr. D. Carruthers (FSA) for item 7	
	Dr. J. Clewley (HPA) for item 4	
	Mr. A. Gresham (Defra) for item 5	
	Dr. P. Grove (DH) for item 4	

Professor J. Ironside (NCJDSU) for item 4
Dr. R. Kosmider (VLA) for item 7

ITEM 1 – CHAIR'S INTRODUCTION

1. The SEAC Chair welcomed everyone to the 100th meeting of SEAC. He explained that Mr John Bassett and Professor David Brown had both left the committee after their second terms of office were completed. The Chair thanked them for their commitment, and the expertise they had brought, to SEAC. The SEAC Steering Group had agreed that no replacements would be sought at the present time. He congratulated Professor Jean Manson on being awarded an OBE recently.

2. Dr Peter Grimley was introduced as the new Secretary to SEAC. The Secretary explained that open meetings allow the public an opportunity to observe the committee at work and provide an insight into how an advisory committee provides independent scientific advice to Government. Government officials with responsibility for transmissible spongiform encephalopathy (TSE) policy may be invited to contribute to discussions. Short summaries of the discussions would be published on the SEAC website.

3. Members were reminded that they are obliged to declare any commercial or other interests they may have at the relevant agenda items. Members were asked to inform the secretariat of any changes to the register of members' interests which had been circulated to them recently. Expense claims should be submitted as soon as possible after meetings and must be submitted within three months of meetings.

4. The 2007 SEAC annual report had recently been placed on the SEAC website. The final report of an independent light-touch review of SEAC had been received and discussed by the SEAC Steering Group. The report would be published on the SEAC website together with a response to the recommendations.

5. Apologies for absence had been received from Professor Margaret Stanley and Ms Diane McCrea. The next SEAC meeting was scheduled for Wednesday 9th July 2008 to take place at the Royal Horticultural Halls and Conference Centre, Westminster, London.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 99 (SEAC 100/1)

6. The minutes of SEAC 99 were agreed as a correct record with the following amendment:

- Paragraph 7, second bullet point, change *"…Institute of Animal Health (IAH)."* to *"…Roslin Institute (RI)."*

7. The committee was updated about transmission studies using isolates from a case of Creutzfeldt-Jakob Disease (CJD)[1] which had been discussed at SEAC 99. Two lines of transgenic mice expressing the human prion protein gene homozygous for methionine (MM) or valine (VV) at codon 129 and two lines of conventional mice had been inoculated with isolates from the case. Transmission has been more efficient to the humanised mice compared with the conventional mice. The molecular characteristics of the abnormal prion protein (PrP^{Sc}) altered on transmission suggesting the patient may have been infected with an unstable TSE strain. Further work was required to characterise the TSE strain. However, it would be difficult to confirm whether this was related to BSE infection unless additional similar cases arose which could be investigated.

8. Members noted that no further information was available about the atypical scrapie case in the flock managed by the Roslin Institute which had been discussed at SEAC 99.

ITEM 3 – CURRENT ISSUES

9. SEAC was informed about the following issues:

- Three cases of variant CJD (vCJD) had been identified in Spain: one each in 2005, 2007 and 2008, with the last two cases reported from the same geographical region. Media reports in Spain had suggested there could be up to five further cases. One of these five cases is a young individual with clinical symptoms of a relatively long duration that had been classified by the Spanish Registry as possible sporadic CJD (sCJD). Although it is possible that this case may be subsequently confirmed as vCJD there were good reasons, which could not be discussed at the present time, for thinking it was not. Four other cases were not considered to be vCJD by TSE experts in Spain. More information would be available as investigations progress.

- The Department of Health (DH) has issued a consultation document on the future regulation of health and adult social care in England. It is proposed that 'high street' dentistry

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

(both private and National Health Service) be registered with a new Care Quality Commission which would ensure that essential requirements of quality and safety are met by healthcare providers. Providers would be required to register and demonstrate that they meet the essential levels of safety and quality required for registration. SEAC agreed to respond to the consultation, welcoming the proposal that the quality and safety of 'high street' dentistry be regulated by the Care Quality Commission. The secretariat would draft a response and circulate it with the consultation document to the committee for comments.

- A large consignment of imported wheat feed contaminated with mammalian and fish material had been identified. Investigations were underway to establish the species of origin of the material and to track the location and the use of the feed. Restrictions had been imposed on animals exposed to the feed until the possible TSE risk could be assessed. The committee noted that this incident showed that feed could become contaminated with mammalian material but also demonstrated that the systems in place can identify such contamination.

ITEM 4 – ASSESSMENT OF PREVALENCE OF SUBCLINICAL vCJD (SEAC 100/2 and SEAC 100/6)

10. The Chair explained that DH had asked SEAC to consider how data from the ongoing National Anonymous Tonsil Archive (NATA) and the completed survey of appendix samples by Hilton *et al.* (2004)[2] might be combined, in order to arrive at a potentially more reliable range of values for the prevalence of subclinical vCJD. In addition, SEAC was also asked what studies might be commissioned to resolve the apparent discrepancy between the data from the two studies.

11. Professor Noel Gill (Health Protection Agency (HPA)) provided an update on the NATA study. Approximately 55 000 NATA samples had been screened by the end of March 2008. None was positive for PrP^{Sc}, although some samples remain to be fully tested. By the end of 2008 and 2009, an additional 16 000 and 28 000 samples, respectively will have been tested. In terms of samples from the 1961-1985 birth cohort, 11 000 samples had been tested. An additional 3000 and 5000 samples will be tested by the end of

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

2008 and 2009, respectively, giving a total number of samples tested in this birth cohort of 19 000 by the end of 2009.

12. Professor Gill noted that the calendar period in which NATA samples had been collected from the 1961-1985 cohort was approximately 10 years later than the period in which appendix samples were collected by Hilton *et al* for the same birth cohort. However, in that birth cohort, the mean age of tonsillectomy patients was approximately four years younger than that of the appendectomy patients. These factors may influence considerations about combining the two datasets. In addition, for reasons which are unclear, the majority of the older patients undergoing tonsillectomy are women (67% in the 1961-1985 birth cohort) but women constitute only 44% of the clinical vCJD cases in that birth cohort. None of the tonsils collected to date have come from known vCJD cases.

13. Professor Gill explained the process by which NATA samples were screened and selected for further investigatory testing. He noted that the mass of tissue tested by the dual enzyme immunoassay (EIA) used to screen the NATA samples is relatively large compared with that tested by immunohistochemistry (IHC), the method used by Hilton *et al*. Dr Jonathan Clewley (HPA) added that the dual EIA system should detect PrP^{Sc} at concentrations between one tenth and one thousandth found in tonsil tissue from patients with clinical vCJD. A comparison of the relative sensitivity of this system with IHC is difficult to make. Thus far, 400 NATA samples tested by the dual EIA had also tested negative for PrP^{Sc} using an IHC method similar to Hilton *et al*. It was planned to test 10 000 NATA samples by both dual EIA and IHC. At SEAC 99, it had been reported that two NATA samples which had given reactive signals in dual EIA tests had also given single bands within the molecular mass range expected for PrP^{Sc} in investigatory western blot tests. Following further investigation, these bands were not considered to be related to PrP^{Sc}.

14. Professor Gill explained that an initial assessment of stored appendectomy samples in hospital pathology departments indicated that about 220 000 samples may have been accumulated in the past five years. Around half may be from the 1961-1985 birth cohort and a quarter from the pre-1961 birth cohort. Thus, it appeared possible to undertake a further survey of appendix tissue.

15. Professor Gill explained that HPA and DH continued to work with the Coroner's Advisory Group (CAG) about establishing an archive

of post mortem tissue collected from Coroners' autopsies. However, the CAG was reluctant for Coroners to collaborate in such an archive.

16. Dr Peter Grove (DH) presented an overview of an algorithm to resolve a perceived discrepancy in the NATA and Hilton *et al* datasets. This included further testing of appendix samples, which could test the validity of the findings from Hilton *et al*.

17. Members agreed that an algorithm to determine how best to approach the studies to estimate the prevalence of infection was extremely useful and should lead to a consistency of approach. A group of experts could inform development of the algorithm, although such a group need not be convened by SEAC.

18. Professor James Ironside (National CJD Surveillance Unit (NCJDSU)) suggested that the data from the NATA and Hilton studies were not incompatible as the confidence intervals of prevalence estimates based on the two studies overlap. He said that the authors of the Hilton *et al* paper had considered carefully the possibility that the three PrP^{Sc} positive samples reported by them may have been false positive results. He said that they were confident that they were not. Extensive research had established that other pathological or inflammatory conditions involving lymphoid tissues did not interfere with the IHC analysis due to upregulation of PrP^{c}[3]. Furthermore, a study of 2 000 tonsils[4] that had used a similar IHC method had not reported false positive results. It is even possible that appendix testing may underestimate the prevalence of infection because it is not known at what time in the incubation period PrP^{Sc} is detectable in the appendix by IHC.

19. A member noted that whilst PrP^{Sc} accumulation had been detected in the three appendix samples, this did not necessarily indicate infection as infectivity *per se* had not been detected. Transmission studies in mice using material from two of the samples are not yet completed. However, owing to the small amount of tissue available negative results from these experiments would not be sufficient to rule out the presence of infectivity. Once complete, the results of these studies would be presented to SEAC.

[3] Hilton *et al*. (2004) Specificity of lymphoreticular accumulation of prion protein for variant Creutzfeldt-Jakob disease. *J Clin Pathol*. 57, 300-302.
[4] Frosh *et al.* (2004) Analysis of 2000 consecutive UK tonsillectomy specimens for disease-related prion protein. *Lancet*. 364, 1260-1262.

20. Members agreed that estimates for the prevalence of subclinical infection based on current data from NATA and from Hilton *et al* are not statistically inconsistent. However, the datasets would become discrepant if NATA continued to find no PrP^{Sc} positive samples. Furthermore, when considering testing of tonsils only, the data from NATA, Hilton *et al* and the study by Frosh *et al*, are consistent as no PrP^{vCJD}-positive samples had been found in all three studies.

21. Professor Ironside noted that the concentration of lymphoreticular tissue in the appendix is much smaller than in the tonsil and if appreciable inflammation had occurred leading to fibrosis then the appendix may have comparatively little lymphoid tissue. Thus, there may be appreciable variability in the level of PrP^{Sc} in the appendix compared with the tonsils of individuals infected with vCJD. Members noted that the appendix is often removed because of a suspicion of acute inflammation, whereas tonsils are mostly removed for elective reasons. Professor Ironside explained that about 33% of appendix samples were excluded by Hilton *et al* because the quantity of lymphoid tissue was limited due to inflammation and fibrosis.

22. Professor Ironside noted that it is also possible that the tissue distribution of PrP^{Sc} may differ between infected individuals of differing prion protein gene codon 129 genotype. The finding that two of the PrP^{Sc} positive appendix samples were from individuals of the comparatively low frequency VV genotype suggests genotype may influence tissue distribution.

23. Professor Ironside explained that 15 out of the 166 UK vCJD cases had undergone tonsillectomy prior to the onset of clinical disease. However, none of the tonsils had been recovered to allow an assessment of the timing of preclinical PrP^{Sc} accumulation in tonsils. Members agreed that there are no human data to determine when PrP^{Sc} accumulation in tonsils occurs prior to the onset of clinical disease.

24. Members suggested that the absence of PrP^{Sc} positive NATA samples so far provides little additional information about the prevalence of subclinical vCJD as too little is known about the pathogenesis of the disease in humans and the timing of PrP^{Sc} accumulation in tonsils. Ongoing studies in sheep could inform on the timing of PrP^{Sc} accumulation in lymphoid tissues of the lower intestine and tonsils and the possible influence of prion protein genotype. However, data from animal studies, although often showing preclinical PrP^{Sc} accumulation in the tonsil, are limited and

are difficult to extrapolate to humans because of differences in pathogenesis of TSE agents between species. Mouse studies which looked at the pathogenesis of classical scrapie and BSE after oral intake of infectious material showed that the distal ileum (the tissue most closely related to human appendix tissue) was PrP^{Sc} positive before other lymphoid tissues.

25. A member suggested that it is possible that BSE may trigger the propagation in humans of different TSE strains with differing pathogenic phenotypes, which could be influenced by host genotype. Such strains may or may not involve PrP^{Sc} accumulation in the lymphoreticular system. In addition, there may be genes, other than the prion protein gene, that may strongly influence the pathogenesis of BSE infection in humans. Thus, it is possible that MM genotype individuals who have developed clinical vCJD may have done so because they are particularly susceptible to that form of BSE-related disease. Other BSE infected individuals may have an infection of a different phenotype with no lymphoreticular PrP^{Sc} accumulation. Dr Jim Hope (Veterinary Laboratories Agency) noted that sheep studies had shown that, following oral challenge, clinical disease could develop in the absence of detectable infectivity in the periphery.

26. Members agreed that the data from NATA and Hilton *et al* should not be added together to give an estimate of infection prevalence as the relative timing of detectable accumulation of PrP^{Sc} in human tonsil and appendix tissue is unknown. However, a range of estimates could be derived by combining data from both studies under differing scenarios with assumptions made about the relative sensitivity of the two approaches to detect subclinical infection. Most combinations of the data would result in lowering the current estimates of the prevalence of subclinical infection. Members considered that the data from Hilton *et al* provides a reasonable working scenario for the prevalence of subclinical vCJD, although it should be borne in mind that appendix testing may underestimate the true prevalence of infection.

27. Members noted that a survey of PrP^{Sc} in human lymphoreticular tissue was underway in Switzerland and a study of the pathogenesis of vCJD in non-human primates was underway in Germany and suggested that the researchers be contacted for an update on progress.

28. Members felt that the NATA study should continue as originally designed, as it was probable that detectable PrP^{Sc} would accumulate in tonsil tissue during the subclinical stage of infection.

Continuing NATA would allow any discrepancy between the NATA and Hilton *et al* approaches to be established or possibly establish whether the approaches might be complementary. The committee did concur with the HPA view, however, that collection and testing of tonsils from children should be discontinued to focus testing on birth cohorts most vulnerable to primary infection. However, it is possible that infections arising from secondary transmission might be detected in the younger age groups.

29. Members suggested that there are three aspects to surveillance of vCJD: the tissue sampled, the calendar time at which tissue is removed and the sample population (age, gender, genotype etc.). At present, the possible discrepancy between the Hilton and NATA studies could be explained by tissue, time and / or sample population. Members agreed that the best approach to understanding the prevalence of subclinical infection, and also to resolving any potential discrepancy in the NATA and Hilton *et al* studies, would be a post mortem study of spleen and brain, as much is known about their involvement in the pathogenesis of TSEs. Such a study may also provide an indication of how prevalence is changing over time. Members expressed great disappointment that it was proving difficult to establish a post mortem tissue archive through the collection of tissues from Coroners' autopsies. Members strongly urged officials to continue their efforts to establish a large-scale post mortem tissue archive.

30. In the absence of progress towards such a post mortem tissue archive, members agreed that further collection and IHC analysis of appendix samples would be useful. The data could be combined with that of Hilton *et al* to increase the sample size and refine the prevalence estimate based on this study. At the same time it had to be acknowledged that appendix testing could underestimate the prevalence of infection. Dr Clewley noted that EIA and western blotting may not be possible on appendix samples stored as paraffin blocks but this remained to be definitively demonstrated.

31. The Chair summarised the discussion, noting that:

    - the experimental techniques used in the Hilton *et al* and NATA studies appear robust.
    - the current working estimate of subclinical infection based on Hilton *et al* should not be adjusted using the NATA data at the present time. The data from the two studies cannot be combined for biological reasons.

- NATA should continue, although consideration should be given to re-focussing this study, for example by stopping testing of paediatric tonsils, as long as the power of the study remained sufficient to detect a determined prevalence of infection.
- extending data from Hilton *et al* by further collection and IHC testing of appendix samples would be informative by allowing the estimates based on Hilton *et al* to be refined.
- uncertainties would always remain about estimates based on either or both studies as the timing and variability of accumulation of PrP^{Sc} in tonsil and appendix tissue in infected humans are unknown at present.
- the best approach now to improving understanding of the prevalence of subclinical infection is a post mortem tissue archive with testing of spleen and where possible brain. SEAC strongly recommends that DH and HPA pursue every avenue to establish such an archive if they wish to obtain improved estimates of the prevalence of BSE infection in humans.
- a SEAC position statement will be produced.

ITEM 5 – UPDATE ON ANIMAL TSEs

32. Mr Patrick Burke (Defra) presented an update on the incidence of BSE in cattle in the UK and other countries, and on the progress of the European Union (EU) survey on TSEs in deer. In the UK, a total of over 183 000 BSE cases have been detected since 1988. The BSE epidemic in cattle peaked in 1992, with over 37 000 confirmed cases and has since declined with 67 cases confirmed in 2007 (60 by active surveillance and seven by passive surveillance) out of over 700 000 animals tested for BSE in 2007. At the peak of the BSE epidemic, about 80% of the clinical suspect cases were confirmed. Subsequently, the confirmation rate for suspected clinical cases has declined to approximately 10%. Two cases of H-type (unusual) BSE have been identified in UK cattle.

33. Analysis of BSE cases by month of birth showed that the incidence of BSE declined as a result of the enforcement of control measures in the UK: the ban on feeding ruminant proteins to ruminants in 1988, the reinforced ban on mammalian meat and bone meal in April 1996, and the EU feed ban in January 2001. There were only 178 BSE cases confirmed in cattle born after the introduction of the UK reinforced feed ban in 1996 (BARB cases) to the end of 2007, of which 18 were detected in 2007. Estimating the prevalence of BSE using the back calculation method showed a steep decline in the prevalence of infection in GB, especially after the introduction

of the reinforced feed ban. The most recent estimate of the mean prevalence in the 2002/2003 birth cohort (the latest birth cohort in which there has been a case in GB) is 5.4 infected animals per million (95% confidence interval, 0.3-24). There has also been a decline in BSE cases in EU Member States with 2671 infected animals detected in 2001, when EU-wide surveillance began with around 10 million animals tested annually, to 171 cases detected in 2007. Low numbers of BSE cases have also been reported outside the EU[5].

34. Mr Burke explained that an EU survey has tested about 10 000 deer for TSEs, including about 398 wild and 503 farmed red deer in the UK, had found no TSE positive animals. The survey will continue for another year.

35. Members asked about the spread of chronic wasting disease (CWD) in the USA. Mr Burke replied that CWD was continuing to spread in the cervid population in the USA.

36. Mr Andrew Gresham (Defra) provided an update on TSEs in sheep and goats. Currently the active surveillance programme has targets to test about 10 000 fallen sheep and 500 goats over 18 months of age and 10 000 sheep over 18 months slaughtered for human consumption. The incidence of classical scrapie in sheep in the UK is in decline, most probably due to the effect of the introduction of the National Scrapie Plan. In GB, only 31 cases were confirmed in 2007 compared with 444 in 2002. Few cases are found in goats. Classical scrapie is also detected in sheep in many European countries and outside Europe, although Australia, New Zealand and South Africa are considered to be free of classical scrapie. Atypical scrapie in sheep is detected mostly by active surveillance. A total of 194 atypical scrapie cases have been confirmed in sheep in GB since surveillance for atypical scrapie began in 2002 of which 30 cases were detected in 2007. Atypical scrapie in sheep and goats has been detected in a number of other countries[6]. BSE has not been identified using differential TSE tests in samples from over 3000 confirmed cases of scrapie in sheep in the UK. One sheep in Cyprus, two in the UK and four from France are under investigation for possible BSE infection. Two further BSE cases were identified with unusual transmission properties in a Defra research project (SE1849) and

[5] Countries where cases of BSE in cattle were reported in 2007: UK, Austria, Canada, Czech Republic, France, Germany, Hungary, Ireland, Italy, Japan, Poland, Portugal, Slovenia, Slovakia, Spain and The Netherlands.

[6] Countries where atypical scrapie in sheep has been reported since 2002: Belgium, Denmark, the Falkland Islands, Finland, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, UK and USA.

are also subject to further characterisation. BSE has been confirmed in one French goat slaughtered in 2002. A UK goat which was originally diagnosed as a case of scrapie in 1990 is under investigation for possible BSE infection.

37. One member asked why an increased number of atypical scrapie infections had been detected more recently. Mr Gresham replied that this is likely to be due to the use of more sensitive detection methods.

ITEM 6 – DRAFT SEAC STATEMENT ON RELAXATIONS TO THE TOTAL FEED BAN (SEAC 100/3)

38. The Chair explained that at SEAC 99, Defra, the devolved Rural Affairs Departments and FSA asked SEAC to consider the potential for TSE infections and epidemics to arise as a result of the possible implementation of various future options for relaxing TSE-related feed controls. Following the meeting, a draft statement was prepared and circulated for comment. Given the number of comments from members, it was decided that the draft statement should be discussed at this meeting to ensure a consensus was reached. The purpose of the statement is to provide an opinion on the TSE-associated risks of the proposed relaxations to the total feed ban.

39. There was discussion around the suggestion that, given the prolonged incubation periods of TSEs, it was unlikely that an emerging TSE in animals or humans as a result of an excessive relaxation of controls would be detected by surveillance before a large number of infections had already occurred. Members agreed that text be included along the lines of "*It is critical, that if regulations are relaxed, suitable surveillance measures are retained. However, it should be acknowledged that because of the long incubation period of TSEs there could be very considerable delay in detection by surveillance of adverse effects, should these ever arise, such that it may be too late to introduce interventions to prevent large-scale infections*."

40. Members agreed that the statement should not focus entirely on the risk from BSE. A paragraph should be included to describe the risk that a new zoonotic TSE strain might emerge as a result of the relaxations to TSE controls. The possibility that the transmissibility to humans of such a new strain could be much greater than that of BSE should be acknowledged.

41. Members agreed to modify a sentence of the text to read "*Relaxation of BSE controls might result in an increased risk of BSE transmission to cattle*."

42. A member asked about the susceptibility of fish to TSEs. A member noted that a study by Ingrosso *et al*[7] reported the rapid clearance of infectious material from two species of fish fed of TSE material with infectivity found in only one fish the day after feeding and no fish 15 days after feeding. There was no evidence of replication of TSE agent in the fish. Mr Burke reminded the committee of a recent European Food Safety Authority risk assessment[8] indicating that the risk of TSEs in fish, either as a result of direct feeding or by amplification of infectivity, is remote. Following discussion, members agreed to wording about the susceptibility of fish as follows: "*Experimental evidence does not show that fish are themselves susceptible to TSEs, although formally it cannot be excluded*."

43. Members agreed that the text should adequately reflect the large uncertainties in calculations to translate the change in BSE risk to an estimated number of new vCJD cases. Some members questioned the value of this approach. It was noted that such an analysis allowed the potential effect of relaxations to TSE controls to be more easily compared.

44. Members suggested that the statement should clearly state that intra-species recycling is very risky and could lead to the emergence of TSE epidemics. It was noted that animal material could be rendered to such an extent that its species of origin becomes undeterminable. The storage and disposal of animal material other than into animal feed, once rendered, also may present risks.

45. Members agreed that the statement should very clearly recommend that the effects of single changes to controls on the effectiveness of whole control regime should be considered rather than only the effectiveness of the control being altered. This would be particularly important if multiple changes to controls were being considered.

46. Members agreed that the statement should highlight the importance of effective monitoring and enforcement of compliance

[7] Ingrosso *et al.* (2006) Scrapie infectivity is quickly cleared in tissues of orally-infected farmed fish. *BMC Vet Res.* 2, 21-28.
[8] EFSA (2007) Health risks of feeding of ruminants with fishmeal in relation to the risk of TSE. *EFSA Journal.* 443, 1-26.

with regulations and note that controls can be difficult to enforce. Additionally, it should be stated that it is important that controls should be in place to stop another epidemic happening again.

47. The Chair asked the Secretariat to revise the draft statement in light of the discussion and circulate it to members to ensure the committee was content with the wording.

ITEM 7 – PROPOSALS TO REDUCE BSE TESTING OF CATTLE SLAUGHTERED FOR FOOD - IMPACT ON RISK TO HUMAN HEALTH (SEAC 100/4)

48. Mr David Carruthers (Food Standards Agency (FSA)) explained that the present requirements for BSE testing of cattle for human consumption were introduced in the UK in November 2005, replacing the over thirty months rule (OTM). Recent changes to the legislation, as proposed in the European Commission's TSE Roadmap, allow Member States to apply to raise the age at which animals are tested provided certain conditions are met. The Commission asked EFSA to consider a range of options for change. Any change to current testing requirements for animals tested for human consumption in the UK would need to be agreed by the FSA board. The FSA and Defra asked VLA to assess the impact on human health of the EFSA options using the VLA BSE control risk model. The outputs from the model will be used to inform the FSA Board of the potential changes in risk to human health from altering the testing regime. SEAC is asked to consider the validity of the inputs and outputs from the model in assessing the possible impact to human health of changes to the BSE testing requirements and also to consider the extent to which BSE testing in OTM cattle was effective in reducing the risk.

49. Dr Rowena Kosmider (VLA) presented an overview of the VLA model. The model incorporates eestimates of the annual number and age of infected cattle that potentially by-pass controls, the infectivity from brain, spinal cord, tonsil, dorsal root ganglia and peripheral nervous system in animals by months before onset of clinical disease and the amount of infectious tissue entering the food chain per infected carcase. The model had been peer-reviewed by experts at Massey University and was considered at SEAC 95 (December 2006). The model has since been updated to include new estimates for prevalence of BSE infection derived using the back calculation method[9], and to take into account

[9] Arnold & Wilesmith (2003) Modelling studies on BSE occurrence to assist in the review of the over 30 months rule in Great Britain. *Proc. Royal Soc.* 270, 2141-2145.

changes to the slaughter population and in BSE surveillance and controls.

50. Dr Kosmider explained that 12 options for the minimum age for BSE testing were considered by raising the age of testing healthy slaughter (HS) cattle from between 30 up to 60 months or of emergency slaughter (ES) and fallen stock (FS) cattle from between 24 up to 60 months. Results from the model showed that compared with 100% testing strategy no additional test positive ES cattle would be missed for the ES control options considered. The options for changing the age of testing for both HS and FS cattle resulted in less than one test positive animal missed for all options when compared with 100% testing strategy. For the current strategy of testing over 30 months HS and 24 month FS/ES cattle the estimated number of test positive animals expected in the 2008/2009 cattle population was a mean of 1.19 for HS, 0.08 for ES and 8.23 for FS cattle. The total annual infectivity entering the food chain for the current testing strategy was calculated to be a mean of 96.45 Bovine ID_{50s} in 2008 decreasing to 34.29 Bovine ID_{50s} in 2009.

51. Dr Kosmider explained that, for illustrative purposes, the impact of missing one to ten BSE positive animals was modelled. The results showed that there would be a small incremental increase in infectivity up to an additional 8.8 Bovine ID_{50s} in 2008 and 3.03 Bovine ID_{50s} in 2009. These figures are very small compared with an estimate that around 11 million Bovine ID_{50s} entered the food chain in 1993[10].

52. A member noted that there are a number of important uncertainties that need to be acknowledged when interpreting these data. Firstly, there is uncertainty in the accuracy of the back calculation model to estimate the prevalence of BSE infected animals that entered the food chain. Secondly, there are uncertainties about the level of infectivity in tissues during the BSE incubation period. It is important to know how well the predictions for the numbers of infected cattle generated by the model fit the surveillance and BSE case data to assess the validity of the model. Previously it had proved difficult to obtain a good fit. Mr Burke responded that there had been difficulties in obtaining accurate dates of birth for cattle born before July 1996 which may have led to these problems. Dr Kosmider stated that for validation purposes, outputs of the model

[10] Comer & Huntly (2004). Exposure of the human population to BSE infectivity over the course of the BSE epidemic in Great Britain and the impact of changes to the Over Thirty Month Rule. *J. Vet. Res.* 7, 523-543.

were routinely compared against surveillance data. Information about the fit of predictions from the model to the observed data would be provided to the committee following the meeting.

53. A member sought clarification regarding the data presented in tables five and six in Annex 2 of SEAC paper 100/4. In table five, the amount of infectivity entering the food chain in 2008 and 2009 was less than 257.35 Bovine Oral ID_{50} (with 95% certainty). However, it was not clear how the number of infected animals entering the food supply was reflected in the figures. In table six, the increase in infectivity with increasing number of infected animals entering the food supply did not appear to be completely linear as may have been expected. Dr Kosmider agreed to respond to these points following the meeting.

54. A member asked why the modelling had not specifically considered the option preferred by the EU of testing at 42 months and 36 months for HS and ES/FS cattle, respectively. Dr Kosmider noted that this option could be modelled relatively quickly. Members noted that in terms of the absolute numbers of infected cattle, fewer test positive animals are missed by increasing the age of testing of HS cattle than increasing the age of testing of ES/FS cattle.

55. Members suggested that the model could be used to look at the change in risk from altering a number of different controls as this was important to consider as had been discussed earlier.

56. The Chair summarised the discussion noting that:
    - clarification should be provided on some of the outputs of the modelling identified during the discussion and on the fit of the model predictions to the observed BSE surveillance and case data.
    - it is important to acknowledge the uncertainties around a number of key parameters in the model such as the infectivity in tissues and the number of infected cattle entering the food chain.
    - it would be useful to consider if the relative contribution of changing the age of testing of the HS and ES/FS cattle simultaneously alters the assessment compared with considering them independently.
    - it is important to keep the assumptions used in the model under review as they may be affected by changes made in the control regime.
    - BSE testing of cattle provides important data on the incidence of the disease and confers some public health

protection. Demonstrating a low level of disease provides reassurance about the effectiveness of controls.

ITEM 8 – HORIZON SCANNING (SEAC 100/5)

57. Members of the committee gave their views on important issues on the TSE science horizon. The following issues were identified:

- the nature and form of the infectious agent and how it causes neurodegeneration remain unclear. Clarification of these issues would help understanding of the disease process and would allow the effectiveness of diagnostic tests and controls to be assessed and new tests to be devised.
- the molecular basis, and classification, of TSE strains and their relationship with host genetics was not well understood.
- the nature of the carrier state, whether infected hosts in a carrier state are infectious or not and what factors influence entry into a carrier state remain to be clarified.
- the full potential and applicability of protein misfolding cyclic amplification and other amplification methods remain to be clarified and developed.
- the development of blood tests and determination of their sensitivity and specificity remains important.
- assessments of the proportionality of BSE surveillance, specified risk material controls and the feed ban given the dwindling number of BSE cases.
- research on the zoonotic potential of the full spectrum of animal TSEs, particularly scrapie strains and new bovine TSEs, to enable quantitative risk assessments.
- assessment of potential routes of TSE transmission, particularly possible transmission via milk and the environment.
- comparison of the characteristics of UK CJD cases and those found elsewhere is important to inform assessment of incubation period, risk factors and the effectiveness of protective measures.
- the possibility that large-scale screening of tissues may reveal an appreciable number of subclinical vCJD infections arising from the large human exposure to BSE during the BSE epidemic.
- therapeutic treatments based on humanised antibodies for infected patients or individuals at high risk of infection.
- identification of genetic factors that modulate susceptibility to TSEs.

- the translation of research on prion diseases to other similar diseases of humans such as Alzheimer's Disease.

58. The Chair added that instead of considering the relaxation of controls that are in place it may be more advantageous to consider instead what controls are required to prevent TSE epidemics arising. A member noted that controls may be maintained but their future management is likely to change with the government exploring the sharing of the cost and responsibility of controls with industry.

59. The Chair noted that TSE research had been very successful as much had been learned: BSE had been very nearly eliminated; the number of cases of human disease is not as large as it might have been; and much was known about how to control TSEs.

ITEM 9 – ANY OTHER BUSINESS

60. The Chair noted that it had been proposed that SEAC adopt a standardised terminology to describe risk and some examples had been set out in SEAC paper 100/AOB. Members noted that risk comprises the probability and impact of an adverse event and in some circumstances it would be desirable to express these parameters separately. Members agreed that SEAC should not be constrained by using a rigorously defined classification of risk but it should carefully consider the use of descriptors of risk when considering draft statements. The Chair asked the secretariat to prepare a note that the committee could refer to in the future of key risk terms. A member suggested an article on risk communication[11] which it may be useful to consult.

61. The Chair closed the meeting, thanking all those who had presented information to the committee and all who attended the meeting.

[11] Calman & Royston (1997) Risk language and dialects. *BMJ.* 315, 939-942.