



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Draft minutes of the open session of the 86th meeting held on 3rd
March 2005

At

The Conference Centre
Holiday Inn Bloomsbury
Coram Street
London
WC1N 1HT

Members:

Professor C. Higgins (Chair)
Dr. D. Brown
Professor G. Bulfield
Professor N. Hooper
Professor J. Ironside (Deputy Chair)
Mr. P. Jinman
Professor J. Manson
Professor I. McConnell
Ms. D. McCrea
Professor G. Medley
Dr. P. Rudge

Assessors:

Mr. A. Harvey (FSA)
Mrs. E. Lawrence (DH)

DA Assessors:

Dr. P. Christie (SEHD)
Dr. A. Douglas (DARDNI)
Dr. M. Simmons (NAW)

Technical Advisors:

Dr. P. Barrowman (Defra)
Dr. S. Dixon (FSA)
Mr. M. Prince (Defra)
Dr. J. Stephenson (DH)
Professor J. Wilesmith (Defra)

SEAC Secretary:

Miss K. Richards

Secretariat: Dr. T. Barlow
Ms. T. Dale
Dr. P. Keep
Dr. C. Ravirajan

Also in attendance: Dr. P. Bennett (DH),
Professor S. Bird (MRC Biostatistics Unit),
Dr. S. Dealler (Lancaster Royal Infirmary),
Dr. A. Ghani (Imperial College),
Mr. A. Tomkinson (NHS Wales), and
Dr. M. Turner (UK Blood Services)
all for item 3.
Professor W. Hill (University of Edinburgh) for
item 4.
Dr. J. Hope (VLA) for item 5.

DRAFT

ITEM 1 - CHAIR'S INTRODUCTION

1. The Chair welcomed members of the public to the tenth public meeting of SEAC and noted this was the first entirely open meeting. The Chair explained that SEAC's policy is to carry out business in the public domain, however circumstances arise where issues may be discussed in closed session, for instance pre-publication research or patient-sensitive medical information.
2. The Chair explained that this was the last meeting to be broadcast live over the internet as part of a one year trial. The success of the trial in terms of potential benefits and uptake of broadcasts would be assessed.
3. The Chair informed members that this would be Professor Grahame Bulfield's last meeting and thanked him for his contributions to SEAC. Apologies for absence had been received from Mr John Bassett, Dr Jackie Chambers and Dr Corinne Lasmezas.
4. The Chair welcomed Dr Peter Bennett (DH), Sheila Bird (MRC Biostatistics Unit), Dr Stephen Dealler (Lancaster Royal Infirmary), Dr Azra Ghani (Imperial College), Mr Alan Harvey (FSA), Professor William Hill (University of Edinburgh), Dr Jim Hope (VLA), Professor Dr John Stephenson (DH), Mr Alun Tomkinson (NHS), and Dr Marc Turner (UK Blood Services) who had been invited to present items to the committee or take part in discussions.
5. Members were reminded of their obligation to declare conflicts of interest at the start of each agenda item. The next meeting would be held on 21st April 2005 in London. The November 2005 meeting would be hosted by the Scottish Executive.

ITEM 2 – APPROVAL OF DRAFT MINUTES FROM SEAC 85 (SEAC 86/1) AND MATTERS ARISING

6. The minutes of the open session of the 30th November meeting were agreed as a correct record. The 30th November meeting reserved business minutes had been circulated to members in advance of the meeting and approved.
7. The Chair reminded the committee that meetings would normally include a regular current issues agenda item but for this meeting the current issues had become substantive items.

8. At the last meeting, SEAC had been informed that a report from the FSA/SEAC milk working group would be provided to the committee at the March meeting. However, the group had decided further work was necessary and would instead report in June 2005.
9. The committee was informed that Defra would present a paper to SEAC at a future meeting on differential diagnosis of BSE. This issue had been raised by the committee at its September and November 2004 meetings.
10. The Chair informed the committee he had received a letter from the Chief Medical Officer for England thanking SEAC for the discussion and position statement on maternal transmission of vCJD.
11. The committee was informed that the SEAC CJD Epidemiology Subgroup had been disbanded and reconvened as the SEAC Epidemiology Subgroup with new terms of reference to include epidemiology on TSEs relevant to both human and animal health. Members noted the membership and terms of reference of the subgroup that had been tabled.

ITEM 3 – IMPLICATIONS OF RECENT RESEARCH ON MODELS OF THE vCJD EPIDEMIC (SEAC 86/2)

12. The Chair informed the committee that an evaluation of the implications of recent research on current understanding of the profile and nature of the vCJD epidemic had been identified as part of SEAC's recent horizon scanning and also requested by DH. Two key issues for consideration had been identified. Firstly, whether current predictions of the vCJD epidemic were realistic or required modification in light of new data. Second, in view of the evidence that vCJD can be laterally transmitted, was a self-sustaining epidemic possible even if primary human infection (ie via infected meat) was completely eliminated. It was envisaged that the committee would conduct an initial consideration of these issues and identify key questions for the SEAC Epidemiology Subgroup. Suggested key questions were outlined in SEAC paper 86/2. To facilitate an initial consideration of the new information, a number of experts had been invited to present new research.

Profile of the primary vCJD epidemic

13. Professor James Ironside (National CJD Surveillance Unit) provided an overview of the clinical features of sCJD and vCJD

and factors that influence these diseases, particularly, polymorphisms at codon 129 of the PrP gene.

14. The cause of sCJD is unknown. It occurs worldwide with an incidence of about 1 case in 1 million people per annum. The disease presents as a number of distinct isotypes differentiated by clinical features and neuropathology. Most cases of sCJD occur in the elderly usually with a short duration of illness but there are large ranges in the age of onset and duration of the disease. Individuals homozygous at codon 129 of the PrP gene (ie. the M/M genotype), are over-represented in sCJD cases compared with the general population.
15. In contrast, vCJD usually occurs in younger people (20-30 years of age) although there is an overlap in the range of age of onset with sCJD. All clinical cases of vCJD have been of the M/M genotype although infection was found in a single asymptomatic individual of non-M/M genotype probably infected as a result of a blood transfusion. The possible phenotype of BSE infection in non-M/M human genotypes is unclear.
16. Professor Ironside explained that analysis of the annual number of onsets of, and deaths from, vCJD indicated a declining epidemic. However, in a survey of abnormal PrP in over 12 000 tonsil and appendix samples¹ (mostly from people of the 10-29 year age group), three appendix samples were positive for the presence of abnormal PrP by immunohistochemical (IHC) tests. This finding suggested that the prevalence of infection may be higher than would be expected from an analysis of the clinical vCJD cases.
17. It was notable that no significant shift in the age distribution of vCJD cases had been observed since the start of the epidemic. It was unclear whether the static age distribution reflected an age-related exposure to BSE, an age-related susceptibility to BSE, age dependent incubation period, under-ascertainment of the disease in the elderly, or was influenced by other, possibly genetic, factors or factors acting in combination.
18. Professor Ironside explained that subtypes of the CJD prion can be differentiated biochemically by the relative mobility and abundance of PrP glycosylated bands in western blots. This suggested that different structural conformations of abnormal PrP may confer strain-specific properties. However, Western blot profiles could not

¹ Hilton *et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol.* 2004 203, 733-739.

definitively differentiate strains of PrP agent. Strain typing bioassays were required for a definitive analysis.

19. In response to a question from the committee, Professor Ironside explained that the samples that tested positive for the presence of PrP in the study of appendix and tonsil tissue had also shown signs of tissue inflammation.
20. Asked whether a shift in the age distribution of sCJD cases had been observed in recent years, Professor Ironside confirmed that no shift had been observed. One member suggested that a comparison of the DNA sequence of the PrP gene from diseased areas in sCJD cases and the PrP genotype of the affected individual may help to determine whether the origin of the disease was related to a somatic gene mutation or the result of protein misfolding. Professor Ironside explained that although a limited number of such analyses had been conducted, there was no evidence to suggest that there were differences between the disease associated PrP sequence and the genotype of the affected individuals. There was insufficient evidence to rule out either a genetic mutation, protein misfolding or even an acquired infection as the possible cause of sCJD.
21. Dr Azra Ghani (Imperial College London) presented projections of the primary vCJD epidemic based on two data sets: data from clinical cases of vCJD and the prevalence of vCJD infection from the tonsil and appendix study. Analysis of clinical case data indicated a statistically significant decline in the incidence of the disease and suggests the size of the epidemic will be relatively small with a maximum likelihood estimate of 70 (95% CI 10-190) additional cases predicted. Modelling work indicated that age-related susceptibility or exposure could explain the static nature of the age-distribution of vCJD cases. An age-related incubation period alone did not, but could not be excluded. Models suggested peak human exposure to BSE would have occurred in the 10-20 year old age group with an average disease incubation time of around 11 years.
22. Dr Ghani explained that naïve analysis of the data from the tonsil and appendix study suggested a prevalence of about 273 infected people per million, or 3800 infected people in the UK population. Uncertainties associated with this estimate included the uncertain validity of extrapolating the results of analysis of samples collected predominantly from 10-29 year old patients to the general population, and the unknown sensitivity of the IHC test used to detect infection. Additionally, it was unclear whether an unusual

IHC staining pattern seen with two of the samples was an experimental artefact or a different form of abnormal PrP, possibly as a result of a different PrP genotype of the patients. Assumptions about the sensitivity of the IHC test altered projections significantly e.g. the estimate of the number of infected individuals would double to around 7600 if a detection sensitivity of 50% was assumed over the course of the incubation period.

23. Dr Ghani explained the significant discrepancy between the prevalence of vCJD based on clinical cases and the tonsil and appendix study could be resolved by inclusion of a carrier state (i.e. subclinical infection) into models of the epidemic. Models adjusted by inclusion of a carrier state predicted a prevalence of infection of around 3000-5400 (depending on IHC test sensitivity) with around 10% (95% CI 5-30%) of infected people developing clinical disease. Additional modelling had included the possibility of a wider genetic susceptibility such that all PrP codon 129 genotypes could be infected. In the absence of clinical data about infection of non-M/M genotypes it had been assumed that non-M/M genotypes would be less susceptible to infection with up to four times longer incubation periods. If it was pessimistically assumed that M/M and non-M/M genotypes were equally susceptible the numbers of additional clinical cases could be up to five-fold higher than predicted.
24. In response to a question from Professor Sheila Bird (MRC Biostatistics Unit), Dr Ghani confirmed that the three positive appendix samples were from patients in the 10-29 year age range. One member added that these individuals could not be identified because of ethical constraints imposed on the study and therefore, the precise ages of the patients could not be determined. Although the lack of further information on the patients imposed constraints on the information the study could provide, Dr Bird suggested that the impact of hypothetical ages of these patients on projections of the epidemic could be modelled. The impact of different carrier status of the patients could also be modelled.
25. One member asked whether the lack of control data either from analysis of UK tonsil and appendix samples collected before 1980 or from samples collected from a BSE-free country would give rise to uncertainties in the projections. Dr Ghani responded that the calculations were based primarily on the clinical case data. However, it was considered important to include the data from the tonsil and appendix study whilst acknowledging the uncertainties in this data set. It was noted that the positive appendix samples were identified on the basis of IHC tests rather than infectivity studies.

Professor Bird expressed caution about predictions based on the clinical case data alone as similarly based predictions of the BSE epidemic substantially underestimated the size of the epidemic. Thus, it would be important to collect information about the possibility of subclinical carriers of infection to refine predictions.

26. One member asked whether the effect of possible age-related incubation time had been modelled. Dr Ghani confirmed that this had been modelled. When considered in isolation, age-related incubation times could not explain the static age-profile of the epidemic. However, it was possible that age-related incubation time may be one factor in combination with other factors that influenced the age-profile of the epidemic. One member asked whether incubation times greater than four-fold that of non-M/M genotypes would have an effect on projections. Dr Ghani responded that longer incubation times would affect the projections but incubation times may then exceed the natural human lifetime.
27. Professor Hooper summarised a recent report by Lasmezas *et al.* (2005)² that estimated the current BSE exposure risk to the human population based on an oral BSE transmission study of two non-human primates. The primate species had been chosen because of the similarities of gastrointestinal system physiology and BSE neuropathology to that found in humans. The animals were M/M at codon 129 of the PrP gene. Following oral administration of 5g of BSE infected brain homogenate, one animal developed clinical disease sixty months later with a vCJD-like neuropathology. Abnormal PrP was found in the tonsil, spleen and intestine. A tonsil biopsy conducted on the other animal at 72 months was negative for the presence of abnormal PrP and the animal was free of clinical signs at 76 months. A comparison of the incubation period with that found in another study of oral transmission of BSE between primates, suggested a species barrier ranging from a factor of seven to twenty for oral transmission of BSE between cattle and primates. An extrapolation based on an infective dose of neural tissue from a cow with preclinical BSE (below the limit of detection of BSE tests) for oral transmission of BSE to humans indicated about 1.5 kg of neural tissue (150 g if a species barrier was considered not to exist) would constitute an infective dose for humans. Such a large dose to humans was considered highly unlikely in view of the specified risk material controls. Thus, the control measures in place were considered effective. Professor Hooper noted that a very small number of animals were used in the study. Adult animals had been used so there was no indication of

² Lasmezas *et al.* (2005) Risk of oral infection with bovine spongiform encephalopathy agent in primates. *Lancet*

possible age-related susceptibility. Additionally, a single dose had been administered thus, a minimum dose for transmission of BSE and the effect of multiple doses could not be determined. An EU funded dose-response study in primates was underway and would be completed in a few years time.

28. One member noted that the findings of an intracerebral transmission study of BSE in primates suggested that the incubation period was significantly shorter in the single young animal inoculated compared with the incubation time in the other adult animals inoculated. It was unclear whether young animals had been included in the EU primate study.
29. In concluding this part of the discussion, SEAC noted that:
 - on the basis of current clinical information, projections of the vCJD epidemic indicate the size of the epidemic will be relatively small. However, there are uncertainties in the current projections, such as the number of possible asymptomatic carriers of infection. Thus, it is not impossible that the epidemic might be somewhat larger than predicted from clinical data alone, although the size of the epidemic is still most likely to be relatively small.
 - whilst limited by, for example, the very low number and the age of animals used, the study by Lasmezas *et al.* (2005) suggests the risk of primary infection has been substantially reduced by control measures introduced to protect the food chain. Thus, secondary infections via medical procedures such as blood transfusion may be the major influence on the profile of the epidemic in the future.

Relationships between prion protein genotype and disease phenotype

30. Professor Jean Manson (Institute of Animal Health) summarised studies conducted by Professor Collinge's group (MRC Prion Unit) using transgenic mouse lines expressing either the M/M or V/V form of the human PrP gene. Although comparisons between lines was complicated by their differing expression levels of the PrP genes, the studies show that after inoculation with either BSE or vCJD, mice of the V/V genotype differ in incubation period, neuropathology and abnormal PrP glycoform compared with mice of the M/M genotype. Although extrapolation of disease phenotype from transgenic mouse lines to humans is unreliable, the findings suggest the clinical presentation of vCJD will differ between individuals of different PrP genotypes. The findings add to the

large body of data that suggest both strain of agent and host PrP genotype determine the phenotype of the disease, and by implication there may be carriers of infectivity with a non-M/M genotype with long incubation periods or who might not ever express clinical disease. Another study examining in detail the relationships between disease susceptibility, phenotype, incubation period and genotype is nearing completion.

31. One member suggested that the genetic modification of the mice may influence the disease phenotype over and above the insertion of a PrP gene. It was noted that in sheep, PrP genotype profoundly influenced susceptibility to scrapie.
32. Professor Margaret Stanley (University of Cambridge) summarised data on Kuru, a prion disease of the Fore people of Papua New Guinea. The Fore adopted cannibalistic funeral practices where family members were ritually cooked and eaten following their death. Female relatives and children prepared the food and also consumed the viscera and brain and therefore were likely to receive a much higher dose of infective agent than men who only ate muscle tissue. Kuru case numbers declined dramatically following cessation of cannibalism. Examination of the profile of the declining epidemic in men, women and children revealed a relatively short incubation time in women and particularly children compared with men, which could be explained by the differential exposure to the Kuru agent. Longer incubation times were also observed in individuals of the M/V genotype compared with homozygote individuals with incubation times exceeding 40 years in some infected individuals of the M/V genotype. The clinical and pathological phenotype of heterozygotes also differed compared with homozygotes. If Kuru was considered to be a model for vCJD, then new vCJD cases would be expected to occur in non-M/M individuals, with a longer incubation time and with a different clinical and pathological phenotype compared with the cases reported to date.
33. Professor Stanley added that secondary transmission of Kuru via medical procedures was highly unlikely in view of the primitive culture of the Fore people. Furthermore, there was no epidemiological evidence for maternal transmission of Kuru. In response to questions about the PrP genotype of the present UK population, the committee was informed that large studies of PrP genotype had been conducted in the UK, which did not indicate large variations between different groups within the population.
34. In concluding this part of the discussion, SEAC noted that:

- there is good evidence that PrP genotype profoundly influences prion disease phenotype, and although most studies have been on animals, this conclusion is likely to apply to humans.
- Kuru could be considered as a good model for aspects of the vCJD epidemic.

Lateral transmission of vCJD and research on minimising risks of transmission via surgery

35. Dr Marc Turner (UK Blood Services) summarised the possible routes of transmission of vCJD through blood transfusion and surgical procedures. The committee were reminded that there had been two cases of probable infection via blood transfusion and although there were no documented cases of vCJD infections via surgery, a theoretical risk of such transmission exists. The likely transmission of sCJD through surgery has been reported. The Blood Services have introduced several measures to reduce transmission risks via blood products. For example, plasma for fractionation is sourced from outside the UK and blood is leucodepleted to remove infectivity associated with the leucocyte fraction. In addition, blood donors who previously received blood or blood products are excluded from donating blood (about 5-10% of the potential donor base). However, as about 5% of any subclinically infected individuals predicted from the modelling studies discussed earlier would be expected to donate blood, the possibility of vCJD transmission via blood from donors with preclinical or subclinical infections is a significant concern. Furthermore, the possibility of a higher prevalence of infection in young adults compared with the general population, due to age-related exposure to BSE or susceptibility to vCJD, was also of concern because of the significant overlap between this population and the blood donor base. Although additional risk reduction measures could be introduced by the Blood Service, any such measures may reduce the donor base to such an extent that sufficient quantities of blood are no longer available.
36. Although people that had received blood transfusions in the UK were prevented from donating blood in the UK, Professor Bird suggested that deferral of donors from France and Ireland should also be considered.
37. Dr John Stephenson (DH) informed the committee about the DH funded research programme relating to transmission risks via

surgery. The aims of the programme were to determine the resistance of vCJD infectivity to inactivation, the protein load on surgical instruments leaving sterile service departments (SSDs), the level of infectivity in human tissue, and the prevalence of disease in the UK population. These data would inform risk assessments on the possible vCJD transmission through surgery. The programme had already provided better estimates of the prevalence of vCJD infection from the tonsil and appendix survey, data on the level of infectivity in various human tissues from vCJD cases, and data on the level of protein contamination on instruments going through SSDs. This modelling had been considered by SEAC at its September 2004 meeting. In addition, research had shown that the vCJD agent is at least as resistant to thermal inactivation as the BSE agent thus, autoclaving procedures in SSDs probably only partially reduce the infective load on surgical instruments.

38. Dr Stephenson updated the committee on the progress of DH funded research relating to the decontamination of reusable surgical instruments. Research to develop rapid, simple screening methods to detect very low levels of abnormal PrP on surgical instruments had shown that the standard ninhydrin test for protein was of little value. A number of other methods including high sensitivity ELISAs, fluorometric detection methods and magnetic acoustic resonant sensors have been developed with detection limits in the 10^{-18} mole to 10^{-12} mole of protein/mm² range. The methods require further development before they could be considered applicable for use in SSDs. Infectivity assays using material bound to wires and steel spheres had also been developed to validate novel inactivation technologies.

39. Dr Stephenson explained that research on the efficacy of inactivation methods for PrP infectivity bound to surfaces indicated that use of alkali autoclaving did not damage high quality instruments. Similar levels of inactivation were found with the use of alkali at high and low temperatures. Use of hypochlorite was inefficient but laboratory detergents removed some but not all proteins from surfaces. Many of the commercial detergents used in SSDs were relatively efficient. One particular detergent removed more than 99.9% of detectable proteins. Additionally, use of thermostable enzymes in conjunction with detergents removed virtually all detectable proteins. Research on gas plasmas showed them to be effective in removal of detectable organic material from the stainless surfaces and cavities of instruments. Research was also underway to examine whether instruments could be coated

with materials that may prevent adsorption of protein onto surfaces.

40. Dr Stephenson informed the committee that a number of research resource centres has been set up to provide the necessary materials to facilitate the decontamination research. In addition, DH funded research and that conducted elsewhere had led to the marketing of a number of commercial products. An Engineering Scientific Advisory Group (ESAC-PR) had recently been convened to consider formal evaluation and implementation of the new technologies within the NHS.
41. In response to a question about the efficiency of SSD decontamination of surgical instruments, Dr Stephenson indicated that steady improvements were being made in this area across the NHS. It was becoming clear that adequate washing of instruments and preventing tissue drying onto instruments were key steps in reducing contamination.
42. One member asked when some of the new technologies would be available to the NHS. Dr Stephenson replied that some of these decontamination methods might be available to the NHS within the next 12-18 months but would need to be evaluated for efficacy and reliability first. ESAC-PR would address the issue of independent validation for new technologies. SEAC strongly endorsed such independent validation.
43. In light of a recent survey in Scotland on decontamination of instruments in dental practices, one member asked whether methods to improve decontamination in dental practice were also under consideration. Dr Stephenson responded that surveys of dental practices had been initiated in England and Wales but, because most dental practices are privately managed, procedures may be difficult to introduce. It is an issue of concern as although the potential risk of vCJD transmission through dental surgery was probably relatively low, the number of procedures is very large. Therefore, in terms of the population as a whole there may be a significant transmission risk. One member added that a number of SEAC members were part of a National Institute for Clinical Excellence group examining vCJD transmission risks via surgery including dental surgery.
44. Mr Alun Tomkinson (NHS Wales) informed the committee about surveillance of single use versus reusable instrument performance for tonsillectomy and adenoidectomy. The committee was reminded that, following SEAC advice, DH announced the

introduction of single use instruments for tonsillectomy in 2001 to minimise the possible transmission of vCJD. However, later in 2001, DH announced the reintroduction of reusable surgical instruments in England for such surgery following reports of post operative haemorrhages. Following this, a research project was set up in Wales to compare the performance of single use versus reusable instruments in tonsillectomy and adenoidectomy to determine if surgery with single use instruments could be as safe as with reusable instruments.

45. Mr Tomkinson explained that in the course of the study operative complications and instrument behaviour were monitored, and a detailed laboratory analysis of single-use instrument design and quality control conducted and compared with reusable instruments. The study showed a number of design and quality control problems with single-use instruments that could have been the source of the increased surgical complication rates. Following these findings, instrument manufacturers were consulted and a design and quality standard for single use instruments set. A surveillance system to monitor the performance of these instruments was introduced. The surveillance showed that post-operative haemorrhage rates with specified single-use instruments were similar to those of reusable instruments. Thus, high quality single-use instruments could be generated but it was important to specify the design and quality of the instruments to manufacturers and introduce a surveillance system to detect potential problems.
46. Members asked about the life-time of reusable instruments and whether single-use instruments were ever reused. Mr Tomkinson replied that the life-time was variable and depended on the type of instruments but some were used in hospitals for up to 40 years. However, single use instruments are disposed of immediately after use.
47. In concluding this part of the discussion, SEAC noted that transmission of vCJD via surgery could be prevented either by use of single-use surgical instruments if managed properly and/or with effective sterilisation and decontamination methods. Such measures could be key to prevention of a secondary epidemic.

Relationships between age and vCJD susceptibility or BSE exposure

48. Dr Peter Bennett (DH) explained that a major focus for DH was the prevention of possible secondary vCJD infections, either by the introduction of universal precautions or by measures that target particular sections of the population on the basis that they may be

of greater risk of carrying infectivity. However, it was vital that any policy decisions to target particular age groups were based on robust conclusions taking account of epidemiological models. Otherwise, there could be a danger of inadvertently making the situation worse.

49. Dr Bennett summarised a paper by Boelle *et al.* (2004)³ that examined age related incubation period, susceptibility, and level of exposure as possible causes of the unusual age distribution of clinical vCJD cases. Models based on data from earlier work by Cooper and Bird indicated that the age profile of vCJD cases could be partially related to differential consumption of BSE contaminated burgers by different population age groups. However, this did not completely explain the high proportion of young cases. By combining age-related exposure to BSE with age-related susceptibility to vCJD into models, Boelle *et al* show that the age distribution could be best explained if susceptibility to vCJD (for a given dose) was greatest in 8-15 year old children. Combining this with differentials in dietary exposure (and assuming that most primary infections arose around the peak of the BSE outbreak in the late 1980s to early 1990s), the people most at risk would now be about 25-35 years of age. This matches the observed distribution of clinical cases.
50. Dr Dealler (Lancaster Royal Infirmary) proposed a different model to explain the static age distribution of clinical vCJD cases. TSEs characteristically have long incubation periods. In animals, the incubation period is usually around 20% of the normal life span if the disease is transmitted from an animal of the same species. If the disease is transmitted from an animal of another species, the incubation period is expected to double. Thus, he argued that in humans, an incubation period of around 25 years for BSE might be expected. However, as early cases of vCJD appear to have a shorter incubation period he suggested that a second wave of cases might be expected with a longer incubation period.
51. To explain these data, Dr Dealler proposed that people may have been infected with BSE when very young, possibly in the first year of life. He proposed that observations of Kuru and animals indicated that the young are infected more easily than the old. As the BSE epidemic might have started around 1970 it was possible that the clinical cases of vCJD seen so far may have been infected as infants around this time from bovine brain included in baby food. No data on the use of bovine brain was available from food

³ Boelle, Cesborn & Valleron (2004) Epidemiological evidence of higher susceptibility to vCJD in the young. *BMC Infect. Diseases*.

manufacturers. However, he suggested that bovine brain had been included in baby food as a common industry practice until 1988 when it was stopped on the recommendation of the Southwood Committee. Thus, Dr Dealler maintained that it is possible that the present peak of clinical cases of vCJD may be a precursor to larger future peaks of people infected as infants later in the 1970s and 1980s.

52. One member noted that there was a gap of about 10 years in the age of maximal susceptibility between the two hypotheses and asked if infection had occurred in the very young then what was the age of the group of greatest risk of infection. Dr Dealler responded that this group would be aged between 16 and 17 years assuming that the use of bovine brain in baby food continued until 1987 and that baby food was used at a very young age as had been the case in the 1970s. Dr Peter Barrowman (Defra) added that an audit of use of cattle derived products in human foods had been conducted in the past by the Leatherhead Food Research Institute. This report was made available to the SEAC CJD Epidemiology subgroup. His recollection was that the report indicated there was no specific evidence for the use of cattle brains for inclusion in baby foods in the period prior to the introduction of SRM controls. Another member noted that the small number of vCJD cases in individuals that had spent time in the UK during the BSE epidemic but as older children or adults, did not support the hypothesis of a role for baby food in the epidemic. These cases implied that infection occurred later in life.
53. A member considered that whether or not the possible route of exposure was via baby food was irrelevant to this discussion as there were no data to support this hypothesis. What was important was to use the epidemiological data to robustly identify the age of initial infection and the population group at risk of being most infective. Dr Ghani added that models on the time of greatest infection produced by Imperial College used robust estimates of numbers of BSE infected animals entering the food supply. These models suggested an age of greatest susceptibility in the 10-20 year old age range.
54. One member noted that, because adult male exposure to the Kuru agent was minimal, male adults with Kuru must have been infected when children to account for the number of male Kuru cases. Additionally, because females received larger and multiple doses of the Kuru agent, the profile of the Kuru epidemic in males and females was very different. Thus, timing of exposure, dose and possibly number of doses all influence the nature of prion disease

epidemics. It was unclear whether multiple doses would act cumulatively.

55. In concluding this part of the discussion, SEAC noted that:

- epidemiological evidence suggests that younger people might be relatively more susceptible to infection. However, the age of greatest susceptibility is currently unclear.
- robust epidemiological predictions supported by data are required to identify at what age people became infected with BSE and the population group at risk of being most infective.

Questions for the SEAC Epidemiology Subgroup

56. The committee agreed with the scope and wording of the questions for the SEAC Epidemiology Subgroup set out in SEAC paper 86/2.

ITEM 4 – INDEPENDENT REVIEW OF ORIGINS OF BARB CASES (SEAC 86/3)

57. The Chair explained that in November 2004, Defra commissioned Professor William Hill (University of Edinburgh) to carry out an independent review into the cause of BARB cases (BSE cases born after the reinforced meat and bone meal ban was introduced in 1st August 1996). Professor Hill had asked to consult SEAC on the scope of the review. SEAC would be asked to comment on the findings of the review once completed. To date 93 GB BARB cases had been identified. In previous discussions, SEAC had agreed that the most likely hypothesis for BARB cases was most likely to be due to feed contaminated in transit prior to the EU-wide feed ban. However, the SEAC ad hoc Epidemiology Subgroup on UK BARBS was involved in a case-control study to examine possible origins of BARB cases. The Subgroup would meet in April 2005 and report interim findings of the study to SEAC at the next meeting.

58. Mr Mike Prince (Defra) updated the committee on the most recent BARB case, identified as part of the TSE surveillance that had been born in October 2001. Although the farm of origin had a history of BSE (a total of 6 cases), the last case occurred in 1994. The case was noteworthy because the animal had been born after the EU-wide feed ban (January 2001). The rations fed to the animal were under investigation. The case would be considered by Professor Hill as part of his review.

59. Professor Hill asked SEAC whether there were issues that should be considered as part of his review that he may not already have identified. It was clear that the clinical signs, neuropathology and age of onset of BARB cases were similar to that of BSE cases born before the feed bans. The geographic distribution of BARB cases appeared to be random, although three pairs of cases with the same farm of origin had been identified. BARB cases occurred almost entirely in dairy cattle. Causes of BARB cases that would be considered included: contaminated feed derived from European sources before the EU-wide ban in 2001; maternal transmission of BSE (although this could not explain the origins of all BARB cases); environmental causes; and a possible genetic disposition to the disease. Other hypotheses that would be considered included organophosphate use and the presence of toxic alkaloids in types of grass.
60. Professor Hill was informed about an EU-funded project looking at possible links between environmental minerals and TSEs. As part of the project, geographical maps were under development showing the concentrations of bioavailable minerals. The geographical distribution of BARB cases and minerals could be compared.
61. It was noted that the incidence of BARB cases was similar to that of sCJD. A member asked whether there might have been a low background level of BSE prior to the epidemic. Professor Hill considered that pre-1970, cases of BSE should have been reported by vets if it was of a similar prevalence to BARB cases. However, members noted that a possible confounding factor in such historical analyses might be the number of animals that present with BSE-like clinical signs that are subsequently not confirmed as BSE cases on post mortem. Historically, the post-mortem level for animals was very low and thus, it would not be possible to determine the level of historical BSE cases. Professor John Wilesmith (Defra) added that modelling work suggested that, under the conditions prior to the feed bans, even a single case of BSE might rapidly give rise to an epidemic.
62. Members asked whether data were available from BSE-free countries with TSE surveillance programmes that may inform assessment of a possible background level of disease. Professor Wilesmith explained that a project was underway to model TSE surveillance in other countries that could provide such data. Members considered it important to focus surveillance on casualty animals as surveillance in this group was most likely to detect an endemic disease.

63. The Chair suggested that Professor Hill contact the Advisory Committee on Animal Feedstuffs (ACAF) as that committee was carrying out a detailed survey of the enforcement of animal feeds. Members noted that the distribution of animal feed was extremely complex.
64. Dr Jim Hope (Veterinary Laboratories Agency) informed the committee of a recent Defra-funded project to sequence the PrP gene of BARB cases and control animals matched for breed and birth cohort. To date, the open reading frame of the PrP gene had been sequenced but preliminary results indicated there were no significant differences in the sequence of the PrP gene between the two groups. The committee welcomed such data and asked that the study be completed as rapidly as possible.
65. Members recommended that infectivity studies on samples from BARB cases should be conducted but acknowledged that samples of sufficient quality may be difficult to obtain.

ITEM 5 – BSE AND GOATS (SEAC 86/4)

66. The Chair explained that in 2002, a single healthy goat had tested positive for a TSE as part of a French surveillance programme. Following further tests, including bioassays, a diagnosis of BSE was confirmed by the Community TSE Reference Laboratory in January 2005. Recently a possible case of BSE had also been reported in Scottish goat killed in 1990.
67. Mr Alan Harvey (FSA) informed the committee that of 140 000 goats tested in the EU since 2002, 111 animals had tested positive for TSEs. Following the finding of BSE in a French goat, the EU had recommended testing of goats over 18 months of age intended for the human food supply. In the UK, all goats over 18 months of age intended for human consumption would be tested on slaughter. The European Food Safety Authority (EFSA) would undertake a risk assessment on consumption of goat meat later in the year that may inform risk management options such as extending specified risk material (SRM) controls. In view of recent EFSA advice issued in November 2004 that milk and milk products from goats are unlikely to present a risk provided milk is sourced from clinically healthy animals, FSA is not advising against the consumption of goat meat and dairy products. In the light of the recent finding of possible BSE in a UK goat, FSA wished to ask SEAC if there was further advice it should impart to consumers and what further information could be collected that might inform the

possible food safety risks. SEAC advice would be provided to EFSA.

68. Dr Hope described the case of possible BSE in the Scottish goat. A three year old male goat born in 1987 had shown clinical signs of TSE in 1990. Histological analysis at the time confirmed the diagnosis as a TSE, at that time assumed to be scrapie. Following the recent confirmation of BSE in the French goat, historical samples of TSE in goats, including the Scottish goat, were analysed as part of the evaluation of an IHC method to distinguish BSE and scrapie in goats.
69. Dr Hope explained the basis of the IHC test and provided an overview of the test results. IHC data of a sample from the Scottish goat were indistinguishable from that of experimental BSE in goats leading to a diagnosis of possible BSE. Although the samples were obviously from a small ruminant, and records kept by the goat owner, the vet and the original histologist were comprehensive, tests were underway to confirm that the sample originated from goat. Brain tissue from the goat had been retained for future research that could include bioassays.
70. Dr Hope informed the committee that a search of VLA archives for samples from TSE goat cases had identified 10 cases of TSE infection between 1984 and 1990. Nine out of the ten cases were indistinguishable from scrapie by IHC. However, in one case, a goat killed in 1984, the IHC results did not rule out BSE and would be further investigated. Additionally, a request made to UK veterinary schools for archived tissues of TSE cases in goats revealed that samples from a further 24 cases going back to 1976 were available for investigation.
71. Members agreed that on the basis of the data presented, the TSE case in the Scottish goat was very likely to be BSE. Members recommended further investigation of this case and other suspect cases of BSE in goats, including strain-typing bioassays possibly in parallel with some non-BSE like TSE goat cases.
72. Members asked if abnormal PrP had been found in the lymphoid tissue of the goat as this would provide additional information about the infectivity of goat tissues. Dr Hope indicated that all the available viscera had been tested by IHC and none had given a positive on IHC testing, although this negative result was not conclusive because of ante-mortem damage to the tissues⁴.

⁴ Notes added post-meeting by VLA

73. Members were informed that feed records kept by the goat owner indicated that the Scottish goat had been fed calf weaning mixture, which had subsequently been highly implicated in the transmission of BSE. The committee considered that this was the likely route of infection and that now MBM is no longer in use the risk of BSE entering the current herd was low. Encouragingly, TSE infections had not been reported in the progeny or subsequent generations of the BSE infected goat.
74. The Chair asked if a theoretical maximum prevalence of BSE in goats could be determined based on the limits of current TSE surveillance. Professor Wilesmith responded that because the UK goat population was very small there are insufficient data from surveillance to estimate an age-related TSE prevalence in UK goats.
75. Members noted that in 2004, the UK was supposed to have tested 500 goat fallen stock for TSEs. However, only 49 had been tested. Defra reported it had plans to increase surveillance in the UK and a legal requirement for goat fallen stock to be tested was planned. The committee welcomed the increased surveillance planned. A member informed the committee that in recent years the goat dairy industry had changed to include increasingly larger and younger herds. In view of this change there may not be accurate information about the UK goat population.
76. A member asked if there was evidence of TSEs in the Swiss goat population. Dr Wilesmith informed the committee that two sheep had been found with scrapie in Switzerland, however there is no active surveillance of goat fallen stock in Switzerland.
77. In relation to the EFSA statement on goat dairy products, members indicated that the nature of sheep and goat milk was different, especially with regard to the white cell content which was higher in goats. As there were no experimental data available on the risk of

1. The IHC test allows provisional characterisation of BSE-like infections in small ruminants and can be applied to CNS and lymphoreticular tissues. However, the only tissues available from animals with experimental BSE tissues for use as test controls were generated by intracerebral challenge. It should be noted that sheep (and presumably goats) infected intracerebrally with TSE agents do not show a wide visceral distribution of infection specific PrP.

2. The UK goat with a BSE-like infection had a limited range of samples of viscera available for IHC. Unfortunately, both the spleen and the lymph nodes showed ante-mortem damage and in neither of the available samples of lymphoid tissue could secondary follicles of germinal centres be clearly recognized. Although IHC was carried out on these tissues, due to the poor quality of the samples, the possible presence, distribution and nature of potential peripheral disease specific PrP could not be determined.

BSE in goats milk some caution was expressed in trying to extrapolate from studies on sheep or cows milk. The committee concluded that there is currently no evidence for a risk from goats milk, primarily because there is no evidence for BSE in the current goat flock, although a risk cannot be excluded as surveillance in goats has been limited.

78. Members considered the risks from goat meat and meat products. Members asked if SRM controls included halal slaughter. The committee was informed that these controls are rigorously enforced by the Meat Hygiene Service, regardless of the method of slaughter.
79. The committee concluded that there was no evidence of BSE in current goat herds, but that this could not be excluded until further surveillance results are assessed. The risk from consumption of goat meat and meat products was therefore likely to be very low, particularly in the light of SRM controls. The committee concluded that on the basis of current evidence it was reasonable for the FSA to continue to not advise against the consumption of goat meat or dairy products. However, SEAC recommended a watching brief should be kept and further information should be considered as it accrues.

ITEM 6 - FINDINGS OF HEIKENWALDER ET AL. (2005)

80. Mr Peter Jinman summarised a paper by Heikenwalder *et al.* (2005)⁵ that showed that, in transgenic mouse models of inflammatory disease, the tissue distribution of scrapie prions and infectivity was altered by chronic inflammation. In the transgenic mice, scrapie prions and infectivity had been detected in inflamed tissues. Abnormal prions and infectivity were absent from these tissues in wild-type mice. The findings suggest that it is possible that concurrent inflammation and prion disease infection may alter the tissue distribution of infectivity such that tissues not normally associated with prion diseases may be infectious. This has implications for the effectiveness of SRM controls to remove potentially infective tissues from animals entering the human food chain. Although, unhealthy animals are identified at abattoirs and do not enter the food chain, it is possible that a transient inflammatory disease may alter the pathogenesis of a prion disease with the animal subsequently being passed fit for human consumption. The Chair informed the committee that the FSA had

⁵ Heikenwalder *et al.* (2005) Chronic lymphocytic inflammation specifies the organ tropism of prions. *Science*. 307, 1107-10.

asked SEAC to consider the implications of the findings of the study for specified risk materials (SRM) controls.

81. The committee noted that the immune system of the mice had been genetically modified resulting in very specific and severe form of inflammation with expanded germinal centres which provide sites for prion protein accumulation. Common inflammatory diseases found in cattle and sheep would be unlikely to produce similar conditions. It was noted that in these mice an element of immune system regulation had been abolished and the inflammatory conditions studied were not equivalent to natural infection. The committee agreed that it was premature to conclude that natural inflammation would alter the distribution of prion infectivity in farm animals. Further work would be required to investigate more fully the influence of inflammation on prion diseases.
82. The committee noted that inspections of animals at abattoirs restricted the entry of unhealthy animals into the food chain. Thus, animals with severe inflammation should normally be excluded from the food chain. Therefore, even if inflammation in farm animals alters prion distribution, SRM and other controls were likely to be effective in minimising risk of infection to humans. Nevertheless, the committee agreed that to minimise potential risk the Meat Hygiene Service should continue to be particularly vigilant in this area.

ITEM 7 - AOB

83. There was no other business to discuss.