



PAPER No: SEAC 78/1

DRAFT

SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Draft minutes of the 77th meeting held on 11th February 2003

At

The Department of Trade and Industry
Conference Centre
1 Victoria Street
London

Members: Professor P. Smith (Chairman)
Professor J. Ironside (Deputy Chairman)
Professor R. Anderson
Professor C. Bostock
Professor G. Bulfield
Dr D. Cunningham
Mr P. Jinman
Professor H. Kimbell
Professor C. Masters
Dr J. Safar

Technical Advisors: Mr P. Soul (Defra)
Dr P. Barrowman (Defra)
Dr J. Stephenson (DH)
Ms A. Conroy (FSA)
Dr S. Dixon (FSA)

Observers: Dr A. Allman (BBSRC)
Dr S. Baxter (SEERAD)
Dr P. Christie (SEERAD)
Dr P. Crook (EA)
Dr A. Douglas (DARDNI)
Dr K. Finney (MRC)
Dr I. Hill (FSA)
Dr D. Matthews (VLA)
Dr J. Nielson (HSE)
Dr M. Simmons (NAWAD)

Assessors: Mr A. Harvey (FSA)
 Dr R. Jecock (DH)

Secretary: Dr C. Boyle

Secretariat: Dr R. Pugh
 Mr M. Pemberton
 Dr C. Ravirajan

Item 1 - Chairman's introduction

- 1.1 The Chairman welcomed Members and the Public to the open meeting, and reminded the Public of SEAC's remit¹ and that the Committee is comprised of 13 Members, each member being an independent expert, and selected through rigorous public appointment procedures.
- 1.2 The Chairman indicated it was the third open meeting of SEAC. The reason for holding public meetings was to provide the public with an opportunity to observe the Committee at work.
- 1.3 The Chairman explained to members of the public that the meeting was essentially a business meeting for the Committee, and asked Members of the public to raise any questions they might have through the Secretariat via the SEAC website (www.seac.gov.uk).
- 1.4 The Chairman welcomed Professor John Collinge (from University College London) who was present to take part in a discussion on agenda item 4, which considered a research paper published from Professor Collinge's research group.
- 1.5 The Chairman informed the Committee that apologies of absence had been received from three Members, Professor A. Aguzzi, Professor R. Carrell and Professor I. McConnell.

Item 2 - Approval of draft minutes from the 14th November SEAC meeting (SEAC 76)

- 2.1 Members agreed the draft minutes from the previous meeting.
- 2.2 Under matters arising, the Chairman reminded the Committee that at the November 2002 meeting it was suggested that a Working-Group should be set up to maintain an overview of the ongoing work relating to attempts to detect abnormal prion protein in milk from cattle experimentally infected with the BSE agent. The Chairman informed the Committee that preliminary discussions between the Secretariat and the FSA had taken place and a working group had been set up.
- 2.3 The Chairman informed the Committee that a letter from the SEAC secretary had been published by the Lancet in December 2003 which corrected an earlier article published by a journalist about the review of SEAC.

¹ The remit of SEAC is 'to provide scientifically based advice to the Department for Environment, Food and Rural Affairs, the Department of Health, devolved administrations, and the Food Standards Agency on matters relating to spongiform encephalopathies, taking account of the remits of other bodies with related responsibilities'.

- 2.4 The Committee sought clarification from the Department of Health under paragraph 7.7 of the minutes as to whether the remit of the Decontamination Science and Engineering Group would extend to the use of private facilities by the NHS. It was explained to the Committee that the issue would be considered and, if appropriate, the remit of the Group would be extended.

Item 3 - Report from the 11th December Sheep Sub-Group meeting

- 3.1 The Committee considered a report² from the Sheep Sub-Group, which had met to discuss unpublished results from an ongoing study at the Institute for Animal Health in the UK. The study is investigating whether sheep from New Zealand (a country considered to be free from TSEs) respond to experimental infection with scrapie and BSE in the same manner as UK sheep, which display distinct PrP genotype linkage with susceptibility to TSEs.
- 3.2 The interim results of the study indicate the experimental transmission of BSE to at least one of the ARR/ARR sheep following intracerebral challenge (ic) with BSE-infected bovine brain homogenate. The incubation period was twice the average incubation period reported for ARQ/ARQ sheep, known from previous studies on UK sheep to be susceptible, challenged by intracerebral inoculation with BSE in the same study. Apart from an unconfirmed case of natural scrapie in Japan, this is the first record of a TSE disease in ARR/ARR sheep.
- 3.3 Members of the Sub-Group were asked to consider if this research had implications for the susceptibility of ARR/ARR sheep to TSEs by natural routes of exposure. The Committee was asked to endorse the statement drafted by the Sub-Group, providing comments where necessary.
- 3.4 At the request of Members, it was agreed that more detail would be included under the conclusions of the statement in relation to the oral challenge studies.
- 3.5 The Committee noted that the conclusions that could be drawn from the experiments conducted to date were dependent on the route of challenge, the numbers of sheep involved and the duration of the study. Members requested that additional information on numbers of sheep involved in both the oral and ic challenge studies to date were noted in the Sub Group statement.

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- 3.6 The Committee noted that very few ARR/ARR sheep had been challenged in experimental studies by intracerebral inoculation of scrapie.
- 3.7 The Committee agreed to endorse the report of the Sheep Sub-Group subject to the changes suggested.

² The report from the Sheep Sub-Group is available on the SEAC website at <http://www.seac.gov.uk/> and is entitled 'Statement on susceptibility of different genotypes in sheep to experimental BSE'.

Item 4- BSE prion propagate as either vCJD-like or sCJD-like prion strains in transgenic mice, expressing human prion protein (EMBO Journal) (SEAC 77/3)

- 4.1 The Chairman welcomed Professor John Collinge, one of the authors on the paper who was present to discuss this work with Members.
- 4.2 The Chairman introduced this item by outlining previous studies conducted at the MRC Prion Unit¹. When transgenic mice expressing a human prion protein homozygous for valine were inoculated with bovine infected brain homogenate, a molecular phenotype similar to that of vCJD was observed. This was interpreted as supporting evidence that vCJD had arisen from exposure to BSE.
- 4.3 To date, all cases of vCJD that have been genotyped are MM homozygous. A recent paper² published from Professor Collinge's laboratory reported research conducted in transgenic mice over-expressing human PrP homozygous for methionine (MM) at codon 129. The transgenic lines were inoculated with bovine infected brain homogenate. One transgenic line (Tg 45) showed PrP biochemical properties and disease pathology similar to those of humans infected with vCJD. Surprisingly, another transgenic line (Tg 35) developed a disease in which the PrP had a molecular signature characteristic of sporadic CJD in humans. Interestingly, these two mouse lines varied in their clinical manifestation of disease following inoculation with bovine infected brain homogenate. Infection of Tg45 mice produced no clinical disease but histological, immunohistochemical and western blotting analysis confirmed sub-clinical infection, whereas the group of infected Tg35 mice included some which showed clinical signs and others which were sub-clinically infected.
- 4.4 Two Members, who were unable to attend the meeting, provided written comments which had been circulated to the Committee and to Professor Collinge prior to the meeting. The Chairman invited Professor Collinge to discuss these comments. The Chairman raised one of the written points which suggested the possibility that the glyco-type assay could have limitations in its applicability to the identification of specific prion strains and their assignment to specific clinical disease forms. It was suggested there was insufficient evidence to show that glycoform signatures could be regarded as an accurate surrogate marker of prion strains.
- 4.5 Professor Collinge responded that he did not understand these comments as two molecular parameters, fragment size shift and ratio of glycoforms, are used to differentiate strains.
- 4.6 Members queried how this research offered confirmation that glycotyping remains a useful tool for human TSE strain differentiation. Professor Collinge considered that this research did confirm that glycotyping can be a useful diagnostic tool as many of the mice in the study displayed a characteristic Type

¹ Collinge J *et al.* (1995) Unaltered susceptibility to BSE in transgenic mice expressing human prion protein. *Nature*, 378, 779-83

² Asante EA *et al* (2002) BSE prion propagate as either variant CJD-like or sporadic CJD-like prion strains in transgenic mice expressing human prion protein EMBO, 21, 6358-66

- 4 signature following inoculation with BSE. Members noted that the glycoform ratios could vary depending on the area of the brain being tested.
- 4.7 Members discussed the potential limitations in the methodology currently used to determine PrP isotypes. Members suggested that it would be useful if alternative conformational or molecular diagnostic tools (thermodynamics of PrP^{Sc}, or the proteolytic sensitivity of PrP^{Sc}) could be used to confirm these new results. Members also noted it would be useful to examine the stability of glycoform pattern during the incubation period. Professor Collinge informed the Committee that this research was underway.
- 4.8 Professor Collinge said he was not suggesting that all cases of sCJD were caused by exposure to BSE, but that the study raised the possibility that some cases of sCJD might be associated with BSE. There are technical difficulties in differentiating PrP^{Sc} Type 1 and 2 (which are both subtypes of sCJD). Professor Collinge suggested that it would be interesting to determine whether PrP^{Sc} types seen in CJD had changed over time, specifically whether there had been an increase in Type 2 with time in countries in which there had been exposure to BSE.
- 4.9 Members agreed that the PrP isotyping is complex. It was recognised that the method of classification of PrP types varies between laboratories. Using the Gambetti methodology, Types 1 and 2 glycoforms defined by the MRC Prion Unit were classed as Type 1; similarly the Type 3 isotype defined by MRC Prion Unit is classed as Type 2 using the Gambetti methodology. For this reason, laboratories using the Gambetti methodology would not be able to differentiate the sub types reported by the MRC Prion Unit. One of the members reported that the epidemiology studies (investigating the incidence of Type 2 sCJD over time in other countries) were underway using the Gambetti form of molecular classification.
- 4.10 One Member raised the point that previous studies in different mouse strains showed that 3 different laboratory isolates of BSE (301C, 301R and 301V) can be produced following passage of a single inoculum from BSE infected brain tissue. Although the phenotypic characteristics of 301C and 301R are similar, there are differences (e.g. in incubation period) between these isolates and 301V. It was also known that non-PrP genes can affect the disease outcome following transmission of BSE to mice. Therefore, it was possible that the differences observed on primary passage of BSE to Tg35 and Tg45 mice could reflect or be influenced by non-PrP genes. Professor Collinge noted that the transgenic mice in the study were derived from outbred strains and agreed this was a possibility. He informed Members that further research was underway to examine this issue.
- 4.11 Professor Collinge agreed that at present, there was no evidence to suggest that more than one strain of BSE existed, but this possibility could not be excluded. He added that research carried out at the Neuropathogenesis Unit showed that the properties of TSE strains could change when serially passaged through different mouse lines. It was possible that strain mutation during serial passage could change the strain properties, and that research was in progress to examine this.

- 4.12 One Member commented that it was surprising that such significant qualitative differences in transmission were evident between the two transgenic lines. He suggested that these differences could reflect or be influenced by the different sites and patterns of insertion of the transgenes. Professor Collinge did not agree and thought it was possible to observe such dramatic differences within similar transgenic lines.
- 4.13 Members discussed the suggestion that this research could reflect an “inoculum effect”. Professor Collinge however stated that the inoculum used in the experiments, with one exception, was sourced from a single brain homogenate.
- 4.14 It was noted that transmission of BSE was not observed in Tg152 mice, while transmission occurred in Tg45 with 9/12 mice showing sub-clinical infection, with a Type 4 molecular signature in all 9 mice. In contrast both clinical and sub clinical infection was observed in Tg35 mice with a Type 2 molecular signature in most of the mice. Members expressed surprise that such varied results could result from the same inoculum in similar transgenic lines. Although not included in the paper, Professor Collinge added that a similar variation had been observed when Tg34 and Tg45 mice had been challenged with a range of inocula.
- 4.15 In response to a query from a Member, Professor Collinge replied that one of the experiments had been carried out using a pooled inocula which had not been glycotyped. Members agreed that cross contamination of the original inocula could affect the results and it was important to eliminate this possibility.
- 4.16 Members queried the inoculum dose given to each animal. It appeared that a low dose was used. Professor Collinge agreed to check the details but replied that the same inoculum had been used in wild type mice with 100% attack rate.

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- 4.17 Members commented that the fact that florid PrP plaques, a neuropathological hallmark of vCJD, could be recapitulated in the brains of the transgenic mice was interesting. The Committee was informed that research was in progress to investigate this further.
- 4.18 Members agreed that the demonstration of subclinical disease was an important finding. Members discussed why subclinical disease had not been detected in previous studies using transgenics expressing human PrP which were valine homozygous. Professor Collinge suggested that previous studies had been terminated at an earlier time-point (before 1,000 days after inoculation). Professor Collinge informed members that archived material from these previous experiments was being re-tested with new more sensitive methods.
- 4.19 The Chairman summarised the discussion noting that this was an interesting and significant paper. The Committee had raised queries about the methodology and Members agreed that the research would need to be repeated and confirmed by other methods before firm conclusions about the significance

of the work could be drawn. Professor Collinge had suggested that the work might indicate that a number of sCJD cases might have arisen from infection with BSE. The Chairman agreed that the Committee had always considered this a plausible hypothesis, but these conclusions were still speculative as the work did not provide strong evidence to support this hypothesis. The research raised general questions about the issue of strain-typing. It was acknowledged that the technical difficulties and differences between laboratories made it a particularly complex issue to progress until some of the technical difficulties had been first resolved. The Committee agreed that the detection of sub-clinical disease had important implications, which had already been recognised and discussed by SEAC. Members agreed it was important that the Committee keep a close eye on further developments in this area.

Item 5 – BSE offspring cull (SEAC No: 77/4)

- 5.1 The Committee was informed that the present UK offspring cull, which came into effect on 4 January 1999, imposes the cull of all offspring born after August 1996 from BSE cases. This regulation was implemented not only to protect the public from potentially BSE-infected beef getting into the food chain but also to secure the agreement of other EU Member States to the resumption of UK beef exports.
- 5.2 The Committee was informed that in order to meet the EU TSE regulations, as applied in other Member states, the UK would have to implement an offspring cull only with regard to offspring born two years prior to the onset of BSE, or offspring born at any time after the development of BSE in the dam. Offspring born outside those two years and aged under 30 months would go into the food chain.
- 5.3 The Committee considered that the available scientific evidence did not suggest that the offspring of BSE cases born more than two years before the onset of BSE in the dam were at higher risk of BSE than the offspring of cattle without BSE. The present UK policy of culling all offspring of BSE cases had been a market measure and included animals for which there was no epidemiological evidence of an increased risk of BSE. The Members therefore considered that there was no scientific evidence to suggest that moving to the EU rule would increase the risk of human exposure to BSE infected animals.
- 5.4 One Member expressed concern about changing the regulation and asked how it would impact on consumers; specifically, the number of offspring that would enter the food chain as a result of the change that was sought. The Member expressed the view that a more precautionary approach should continue.
- 5.5 The Member also requested an update on an issue relating to a previous SEAC discussion about the preservation of animals where the offspring had developed BSE, but the dam had not. Dr Matthews reminded the Committee that there had been two proposals. One proposal was to preserve the offspring for research purposes to study throughout their natural life. However, when SEAC had previously been asked for its advice, it had considered that the cost of such a study was disproportionate. The other proposal was to keep the dam alive,

where an offspring had been born after 1996 that was positive. A research proposal had been submitted to Defra to study the dams of BSE infected offspring born after 1996. The Committee was informed one such dam was currently housed at the VLA, but was unclear as to the value of a study with as yet no clearly defined hypothesis.

- 5.6 The Committee considered that consumers would continue to be protected by the ban on feeding mammalian meat and bone meal (MMBM) to all farmed livestock, the removal of specified risk material (SRM) in abattoirs and by the Over Thirty Month (OTM) rule.
- 5.7 Summarising, the Chairman noted that the UK comprehensive offspring cull had originally been put in place as a market support measure but the Committee saw no scientific grounds for maintaining the current UK policy for culling offspring. The Chairman asked Defra to report the number of offspring likely to enter the food chain as a result of the change.

Item 6 - vCJD update

- 6.1 The Committee conducted its regular review of epidemiological information on vCJD. The Committee was informed that the total number of definite or probable vCJD cases in the UK, as at 11 February 2003, was 130, six of whom were still alive. Of this total, 72 were male and 58 female cases. The mean age at death was 29 years with a range of 14 to 74 years, and the mean age at onset was 27 years, with a range of 12 to 74 years. The median duration of illness was 14 months with a range of 6 to 39 months. It remained the position that all of the cases tested for the prion protein (PrP) genotype (111 in total), were Methionine/Methionine homozygous at codon 129 of the PrP gene. No other polymorphism or pathogenic mutations had been identified in these patients.
- 6.2 The Committee noted the six vCJD cases in France, one in the Republic of Ireland, one in Italy, one in the USA and one in Canada. None of the cases from France, or the case from Italy, had a history of residence in the UK. The cases reported in Ireland, US and Canada had a history of UK residence in the late 1980s.
- 6.3 The Committee noted that the number of onsets per annum peaked in 1999 (over 27 patients were detected in 1999) and then showed a declining trend. Similarly, the figures also showed that the number of deaths per annum of vCJD patients increased to a peak in 2000 and then declined.
- 6.4 The Committee noted the results from an analysis from the Public Health Laboratory Service from January 1994 to January 2003, which showed that the observed and expected onsets and deaths displayed an exponential growth (where it is assumed that the numbers were to go up by a constant percentage each year). The current analysis showed that the trend in the number of vCJD cases had increased, on an average, by 13% per year since 1994 for onsets and 15% per year for deaths since 1995. However, the statistical analysis showed that in a study of onsets and deaths by quarter, a model, which allows

for a departure from an increasing exponential trend (a quadratic trend on a logarithmic scale), appeared to be a better fit to the data than a model which does not allow such a departure.

- 6.5 The age at death had so far remained stable, contrary to what might be expected given that most exposure to BSE ceased in the early 1990s. This finding is consistent with different age-specific susceptibility or exposure. The epidemic curves (quadratic model) were compared in those born before 1970 with those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves. The main difference is due to the fact that in the 1980s cohort no deaths were seen prior to 1999. The reasons for the differences between cohorts are unclear and need further investigation, but could be partly explained by differential age-specific exposure or susceptibility to BSE. It remains unclear whether the trend in deaths for the 1980s cohort has peaked or even slowed, as there are six cases still alive at the end of January 2003, which are part of this cohort.
- 6.6 The Committee was informed that although the mortality rate was no longer increasing exponentially, it was premature to conclude that the epidemic was in decline. The apparent slowing in the death rate could be due to a possible decline in case ascertainment. However, this was considered unlikely. Although there was an increase in referral rates after 1996, there had been a decline in referrals to the CJD Surveillance Unit in more recent years, with the lowest rate of referral occurring in 2002. The decrease in referrals in 2002 may be due to the improved quality of referrals i.e. most patients referred have some form of CJD, thus implying that clinicians are more experienced in diagnosis.
- 6.7 However, the Committee noted the figures of autopsy rates per annum from 1990 to 2003 (as at February 2003) for all referrals, sCJD and vCJD. The autopsy rate had declined in all referrals including sCJD and vCJD after 2000 and reached the lowest level in 2002. Members noted that the examination of brain tissue during autopsy is crucial for definitive diagnosis. The Committee had discussed this issue previously and had noted the importance of the relationship of the clinician with the patient and family, as the final decision as to whether or not to perform an autopsy lies with the relatives of the patient.
- 6.8 The Committee was informed that although the number of sCJD cases has increased since surveillance began (with current incidence of approximately 1/million/year), there is no specific evidence of an increase in the number of sCJD cases associated with the emergence of BSE. Members noted that the increase in the number of deaths from sCJD is not unique to the UK, but has increased in a number of countries, including countries, which do not have BSE. For example, the USA has similar frequency of sCJD to that in the UK and Australia has a higher incidence of sCJD than the UK. For this reason, the increase in numbers was considered to be due to better ascertainment, particularly as the increase in numbers was primarily related to an increase in the elderly population.
- 6.9 Members were informed that the number (and percentage) of sCJD cases in the UK which are of the Methionine/Methionine (MM1) homozygous PrP isotype has remained reasonably constant over the last decade, but has fluctuated in

other EU countries over the same time period. There is therefore no evidence of an increase in this isotype due to a BSE effect.

- 6.10 The Committee was informed that Oxford University has recently completed a random screening programme of motor vehicle accident victims for the presence of PrP^{Sc} in the cerebral cortex. Meanwhile, Nottingham University has investigated elderly patients for the possible presence of subclinical disease. However, the Committee noted that a limitation in taking these studies forward is the lack of a very sensitive diagnostic test to detect prion proteins in tissues of preclinical patients.
- 6.11 One Member queried whether it is now possible to determine a mean incubation period given that the peak exposure to BSE is likely to be around 1989, and the peak of the CJD epidemic could be around 2000. Professor Ironside considered it premature to draw conclusions as yet, as some cases of Kuru were thought to have an incubation period of 40 years or more. The variation in incubation period could be due to different PrP genotypes and genetic backgrounds. Members noted that Kuru was transmitted from human to human transmission and the species barrier effect is considered an important determinant when considering incubation periods.
- 6.12 Members queried if the trends in sCJD in Europe and other countries had been analysed statistically. The Committee noted there were two ongoing studies funded by the EU. The Committee agreed it would be useful to invite an expert in the field of sCJD surveillance to a future SEAC meeting in order to provide an update on this research.

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- 6.13 The Committee was informed that details of the analysis of vCJD incidence were available on the National CJD Surveillance Unit website: www.cjd.ed.ac.uk. The Committee agreed that it was still not possible to forecast longer-term trends of the vCJD disease with any certainty.

Item 7 - BSE epidemiology in the UK and other EU Member States (SEAC 77/5)

- 7.1 Mr Peter Soul (Defra) presented an information update on BSE epidemiology in the UK and other EU Member States.
- 7.2 The Committee was presented with data on the number of clinical suspects identified since 1993 in GB. These data showed a sharp decline over time, with 40% decline in cases from 2001 to 2002. Members were also informed that the average age at onset of disease has increased over time.
- 7.3 Members were informed that the actual decline in the epidemic had departed from the predicted decline, based on the modelling work undertaken by the VLA. It was noted that this was probably due to the delay, caused by the foot and mouth disease epidemic, of the slaughter of cattle under the Over Thirty Month Scheme (OTMS). Despite this, the epidemic still showed a steady decline.

- 7.4 The Committee was informed that incidence of BSE, categorised according to date of birth cohorts, has declined since 1994. Assuming animals are exposed early in life, this provides further evidence for a significant reduction in exposure since 1995.
- 7.5 The Committee noted that an active surveillance programme had been in place since July 2001 following an EU legal requirement. The cumulative BSE cases identified by clinical signs and active surveillance from January 1997 to December 2002 showed a sharp decline in the UK. However, an increasing trend in some other Member States was evident.
- 7.6 The Committee noted data on BSE cases born post August 1996 (BARBs²) across the Member States. As at January 2003, 31 BARB cases had been diagnosed in Great Britain. Some Member States had approximately double this number. When the data were presented in terms of BARB cases per million adult cattle, some other Member States had greater rates of BARBs than Great Britain. It was noted that, in comparison with other Member states, Great Britain is currently not testing as many cattle, however, the rates in GB were lower than in some other states even after allowing for this.
- 7.7 Members were informed that BARB cases had longer incubation periods compared with previous cohorts, and this suggested a low level of exposure. Members also noted that the geographical distribution of BARB cases was different from that of BAB² cases – which had been linked to cross-contamination of cattle feed in mills, which also processed pig feed. The greatest incidence of BAB cases occurred in eastern England. In contrast, the incidence of BARB cases was more widespread, with predominance in counties in which dairy herds were concentrated. This suggested a more random distribution of cases. Members were informed that the GB BARB cases were currently being investigated further in order to try to determine the cause of such cases, such as non-compliance of control policies. This included lesion profiling in order to ascertain whether there were any pathological differences between these animals and earlier different cohorts.
- 7.8 A Member sought clarification on the difference between passive and active surveillance. Mr Soul informed the Committee that passive surveillance corresponds to the clinical cases that are notified to the department by the producer or the producer's vet. Active surveillance in the UK currently comprises proactive surveillance testing of 3 specific animal populations: "Fallen stock" – animals which die on farm and are over 24 months; "Casualty Animals" – animals over 24 months which are taken out of the herd for

² In the UK it has been illegal to feed ruminants with ruminant derived protein since July 1988 and to feed any farmed livestock, including fish and horses, with mammalian meat and bone meal (mammalian MBM) since 04 April 1996. Any animal born after July 1988 is referred to as a BAB case (born after the ban) and any animal born after 1 August 1996 is referred to as a BARB case (born after the real ban).

slaughter due to some other disease or ailment; and different populations of animals slaughtered under the OTMS.

- 7.9 One Member queried the number of positive animals under 30 months that had been identified positive by active surveillance. These animals would otherwise get into the food chain. Members were informed that the active surveillance which included testing of fallen stock and casualty animals aged over 24 months had identified positive BSE cases only in animals aged over 30 months and these animals would not be permitted in the food chain under the OTMS.
- 7.10 One Member highlighted the fact that more infections were detected through active surveillance than via clinical case reporting. Given that the future trend of the epidemic was based on case reporting, the Member asked whether any research was being undertaken to establish why such differences occurred. The Committee was informed that such a research study was not included within the current Defra research programme. The Committee noted that to undertake such a study would be very complex and costly. Dr Matthews believed that the discrepancy related to case recognition; many producers believed that BSE was a historical problem and no longer recognised some of the earlier clinical signs. Dr Matthews also expressed the view that fallen stock had always existed on farm, but had not been recognised as potential BSE suspects.
- 7.11 One Member commented on the number of BSE cases in animals born after 1996 in some EU Member States. Given that the feed ban was introduced in August 1996, concern was expressed about other Member States not implementing EU legislation. The Committee was informed that the EU wide comprehensive feed ban did not commence until January 2001. As such, it would be in the region of five years, after the introduction of the ban, before the effects are fully evident. Members were informed that the EU Commission considers the control measures now in place, coupled with the testing programme, provide adequate risk reduction measures for the consumption of beef from animals over the age of thirty months. In respect of enforcement, the Commission's Food and Veterinary Office undertake audits of Member States to ensure compliance with EU legislation. The Committee was also informed that equivalent measures would apply under EU trade rules to those non-EU countries that export their meat products to EU Member States.

Item 8- Departmental Research Updates (SEAC 77/6)

Update on the DH funded research programme

- 8.1 Dr John Stephenson provided an update on the DH research programme. Planning for a clinical trial for quinicrine was underway and a Clinical Trial Steering Committee was currently being set up. It was anticipated that recruitment of patients for the trial would have started by summer 2003.
- 8.2 The Committee was informed of a number of DH funded surveys which were ongoing or due to start this year:
- A retrospective survey of tonsil/appendices is underway.

- The Chief Medical Officer had approved a prospective study on 5000 tonsil samples, which was due to start later in 2003.
- A retrospective survey of atypical dementia across the UK is underway. Results to date do not suggest evidence of under ascertainment of vCJD.
- The British Paediatric Survey Unit (at Cambridge) is investigating progressive intellectual and neurological diseases in children under 16 years of age. To date there is no evidence of previously undiagnosed cases of vCJD in this cohort.
- A further survey has been commissioned aimed at determining the exposure of haemophiliacs; and a study of children with severe combined immune deficiency is under consideration.

8.3 One Member pointed out that it was prudent to conduct the tonsil surveys, but highlighted the fact that most tonsillectomies are performed in children under 10 years of age, while the average age of patients with vCJD is 27 years. It was suggested that spleen tissue could be analysed. Dr. Stephenson commented that this strategy had been considered, but the low numbers of splenectomies carried out each year would be unlikely to yield significant results.

8.4 DH have initiated a planning process to allow screening of human blood to become operational once a diagnostic assay to detect prion protein in blood from preclinical cases of CJD becomes available. The contingency planning was being conducted by a Sub Group of the Committee for the Microbial Safety of Blood and Tissues for Transplantation, and it was anticipated that the contingency plan would be completed by the summer of 2003.

8.5 Members were informed that a Science and Engineering Decontamination Group has been established. This group will facilitate the implementation of research findings into practical healthcare setting. The group will meet in shadow form until it receives appropriate sponsorship.

8.6 Members were informed of reviews by the MRC/DH Research Advisory Group of ongoing research on diagnostics, structural biology, molecular biology and epidemiological research. The aim of the review was to ensure that there are no gaps in the ongoing programmes.

Update on Defra funded TSE research programme

8.7 Dr Peter Barrowman provided an update on the Defra funded research programme. The research budget for the next two financial years (03/04 and 04/05) would be in the region of £16.6m. This programme does not include the funding for surveillance. It was anticipated that there would be a reduced requirement in 05/06 due to the completion of large-scale projects. A statement of the Department's research needs will be outlined in the Science and Innovation Strategy Document, which is due to be published in May 2003.

8.8 Members noted that the primary focus would remain on TSEs in sheep. Research into BSE in cattle would continue, but would adapt to meet the requirements of policy issues. Members noted that ongoing research in cattle included studies to determine the minimum oral dose. Epidemiological studies would continue, but much of this would be continued under the surveillance

programme; of particular interest however would be the investigation of BARB cases. Work on developing tests, which can monitor feed for ruminant protein, was also underway.

- 8.9 The Committee was informed of a number of key areas of research. Members noted that studies on the distribution of infectivity (pathogenesis) in sheep infected with scrapie and experimental BSE were ongoing. The development of diagnostic tests remained a major focus. There was a requirement for preclinical and differential diagnostic tests to discriminate between experimental BSE and scrapie in sheep. There is ongoing work on strain stability of TSEs following serial passage in different species. This area of work was particularly important, especially in the light of the work discussed with Professor Collinge (agenda item 4).
- 8.10 Members were informed that Defra will commission research to determine if the breeding strategy under the National Scrapie Plan (NSP), which aims to reduce and eliminate TSEs in sheep, will affect the commercial viability of progeny. Work will also be carried out to ascertain the impact of the NSP breeding strategy on rare breeds.
- 8.11 The Committee was informed that a report from the Workshop on TSEs and the environment, which was held last year, was available on the Defra web-site. Independent experts in soil and environmental science attended. Members were informed that a key conclusion from the Workshop was a requirement to develop appropriate methods to detect infectivity or PrP^{Sc} in the soil environment. Although no funding is available to support this work, one ongoing project is investigating the effect of exposing TSE free New Zealand sheep to indoor and field environments, which have previously been exposed to TSE-infected sheep. Another ongoing study is examining the persistence and migration of infectivity/PrP^{Sc} in the soil environment.
- 8.12 One Member queried whether the tests currently being validated under the EU ring trial (paragraph 4.3, paper 77/9) were being evaluated against brain material of known age of infection. It was considered important to determine the sensitivity of diagnostic tests at different stages in the incubation period. However, Members noted that in addition to the fact that availability of tissues from the pathogenesis studies is limited, the issue of sensitivity was more complex, in that the relationship between PrP^{Sc} and infectivity is not known. Members also noted that the current EU validation trial is using brain tissue, whereas the development of tests for use on accessible tissues, which would be useful for preclinical tests, are still in experimental stages.
- 8.13 The Secretary informed the Committee that the Defra Science and Innovation Strategy had been sent out for consultation. Members were asked to provide comment on the scientific aspects of the document, and were not being asked to comment on policy.

Action: SEAC Members