SEAC

Spongiform
Encephalopathy
Advisory
Committee

ANNUAL REPORT 2004

CONTENTS

Foreword

I would like to introduce this report by thanking my predecessor as SEAC Chair, Professor Peter Smith, for his many years of distinguished service to the committee and wish him well for the future. In addition to Professor Smith's retirement as Chair, the membership of the committee has changed considerably over the past year. Professors Adriano Aguzzi, Robin Carrell, Chris Bostock and Harriet Kimbell have stepped down from the committee having made many important contributions to SEAC during their periods of service. As well as a new Chair, ten new members were appointed to SEAC in 2004. I am sure that, like me, they are looking forward to the challenging and complex issues SEAC will be considering in the forthcoming years.

In 2004, initially under Peter Smith's Chairmanship and then under mine, SEAC discussed a wide range of issues relating to transmissible spongiform encephalopathies.

The committee provided advice to the Department of Health on the implications of the first two presumed instances of blood transfusion associated transmission of the vCJD agent and on the potential risks of transmission of vCJD via surgical instruments. At the request of the Chief Medical Officer for England, the committee also considered the potential for transmission of vCJD from mother to child.

The committee advised the Food Standards Agency on the impact of replacement of the Over Thirty Month Rule with a BSE testing regime and on possible risk reduction measures should BSE be found to be present in the national sheep flock. SEAC also advised the Agency on a survey of historic butchery practices and on the potential risks of chronic wasting disease in UK deer.

Advice was provided to Defra on an assessment of the effects of tallow separation and solvent extraction on the BSE agent during the rendering of cattle carcases and on the safety of collagen sourced from the hides of UK cattle.

The committee received presentations from a number of researchers including an overview of CJD surveillance in Switzerland and an investigation of possible atypical cases of BSE.

The work of the committee continues to attract a great deal of interest from the public, the media and the scientific community. SEAC continues to hold open meetings to provide an opportunity for interested parties to see

how the committee's advice is formulated. In addition, this year the committee took part in a trial of broadcasting meetings live over the internet. This initiative has opened up the committee's deliberations to audiences throughout the UK and also internationally. The trial will continue into 2005 when it will be evaluated to determine whether it is worthwhile and sustainable in the longer term. In November 2004, SEAC held its first open meeting outside of London, which was hosted by the National Assembly Government of Wales in Cardiff.

The committee continues to be reliant upon access to early research findings and I would like to thank the researchers who have kindly presented their work to the committee prior to publication. Finally, I would like to add my thanks to the work carried out by the committee's secretariat without whose efforts the committee would not run so smoothly. In particular, I would like to thank Catherine Boyle who has moved to a new post at DEFRA and welcome her replacement as Secretary, Kate Richards.

Professor Chris Higgins

Chair of SEAC

About the Committee

Background

1. SEAC is an independent expert advisory committee with the following terms of reference. To:

advise on Transmissible Spongiform Encephalopathies (TSEs) at the request of:

Department of Environment, Food and Rural Affairs (Defra)
Department of Health (DH)
Food Standards Agency (FSA)
Scottish Executive
Welsh Assembly Government
Northern Ireland Executive

provide independent scientific advice on food safety, public and animal health issues relating to TSEs taking account of the remits of other bodies with related responsibilities.

provide scientifically based assessment of risk from TSEs to public and animal health and food safety taking appropriate account of scientific uncertainty and assumptions in formulating advice. The committee will convey the nature and extent of such uncertainties with the advice.

advise on important general principles or new scientific discoveries in TSEs to assist in the identification of new or emerging TSE risks for public or animal health and food.

advise on the scientific basis and risks associated with the introduction of new control measures or the reduction, phasing out or withdrawal of current control measures which are in place to protect public health or animal health from TSEs.

identify where research is desirable to reduce the scientific uncertainty and inform the assessment of public and animal health and food safety risks relating to TSEs.

2. SEAC evolved as a reconstitution of the Tyrrell Committee, which in turn emerged from the Southwood Working Party. The Tyrrell Committee and the Southwood Working Party were the bodies that originally advised the Government on BSE related issues. SEAC had its inaugural meeting on 1 May 1990 and since then has been the principal source of independent advice to the government on matters relating to transmissible spongiform encephalopathies (TSEs). A glossary of the abbreviations used in this report is given at Annex 1.

3. SEAC is a public body. Members are appointed to the committee in accordance with the code for public appointments issued by the Commissioner for Public Appointments. This is based on the Nolan Principles, which aim to ensure fairness and transparency in appointments. SEAC is funded by Defra, DH and the FSA.

4. It is usual for the committee to meet five or six times a year to formulate advice to Ministers on scientific aspects of TSEs. It is standard practice for Ministers and the Board of the FSA to consider SEAC's advice when formulating public and animal health policies relating to TSEs and to publish the advice from SEAC. Committee discussions may be initiated by the following:

    - specific requests from Government Departments and officials for advice,
    - results of new research,
    - requests from a member of the committee, or
    - enquiries from members of the public.

5. In 2004, the committee met on 25th February, 29th April, 24th June, 28th September and 30th November.

Openness

6. SEAC has worked to increase the openness and transparency of the way it operates. In September 2002, the public was invited to observe the committee at work by attending open meetings. In September 2004, SEAC became the first Advisory Committee to broadcast open meetings live on the internet, with recordings available to view after the meetings. In November 2004, the first SEAC open meeting outside London took place. The meeting, held in Cardiff, was hosted by the Welsh Assembly Government and included a public question and answer session.

7. The committee publishes most of its advice and reports of meetings on the SEAC website (www.seac.gov.uk). The website provides information on the SEAC Chair and members as well as meeting agendas, papers, minutes and statements. Within two working days of a meeting a summary of the meeting is placed on the website.

8. There are occasions when certain information, such as pre-publication material or confidential medical data cannot be discussed in open session. These data are considered in a reserved business session. However, from November 2004 summaries of the issues under consideration in reserved business are included on the SEAC website before and after meetings. Once the information being considered has been published, full details of the discussion are released into the public domain.

Membership

9. Members of SEAC are usually appointed for a period of between one and three years. The Commissioner for Public Appointments Code considers that renewal for a further three years, but not longer, is permissible. During the period covered by this report, SEAC comprised a wide range of expertise including, TSE science, epidemiology, neurology, neuropathology, veterinary science, genetics, risk assessment, public interest, molecular microbiology and public health practice. The membership of the committee in 2004 is given at Annex 2.

Code of Practice for Members

10. The committee agreed a revised Code of Practice in July 2003, available at www.seac.gov.uk/CoP_index.htm. This contains guidance on openness, confidentiality and the provision of information on commercial and non-commercial interests. Information on the indemnity offered by Ministers to members of SEAC and its subgroups, in connection with the performance of committee duties, is included. This indemnity is given at Annex 3. The Code of Practice incorporates the seven principles of public life and gives specific guidance on publication of work by SEAC members, conflicts of interest and confidentiality.

Conflicts of Interest

11. Details of commercial and non-commercial interests of SEAC members that may conflict with their responsibilities as members of the committee are placed in the public domain. The register can be

found at Annex 4. In addition to the register of members' interests, members are asked, at the beginning of each meeting, to declare any conflicts of interest with respect to individual agenda items.

Secretariat

12. The secretariat co-ordinates the work of the committee, prepares meeting papers, minutes and statements, and arranges the financing of the committee's activities. Details of the secretariat can be found at Annex 2.

Subgroups and *ad hoc* working groups

13. The Chair of SEAC may authorise the formation of subgroups and *ad hoc* working groups to undertake specific tasks. There is considerable flexibility about how such groups are convened but all have specific terms of reference and are required to report to the main committee. Members of SEAC may serve on these groups and experts not serving on the committee may be invited to provide additional specialist expertise. Use of such groups has allowed the committee to delegate the initial consideration of some of the highly specialised issues.

14. Over the past year the SEAC/FSA Risk Assessment Group on Over the Thirty Month Rule (OTMR) changes and the SEAC sheep subgroup reported to the main committee. The membership and terms of reference of the SEAC/FSA Risk Assessment Group and the membership of the SEAC sheep subgroup are given at Annexes 5 and 6, respectively.

Topics Considered

A. CJD and Public Health

vCJD update

15. In February, April and September, SEAC received updates on the number of variant Creutzfeld-Jacob disease (vCJD) cases in the UK and worldwide from the National CJD Surveillance Unit. By 28th September 2004, the total number of definite and probable vCJD cases in the UK was 149. All the cases tested were of the same genotype (methionine homozygous) at codon 129 of the prion protein (PrP) gene.

16. As in previous years statistical analysis of the number of deaths from vCJD continued to show evidence that the epidemic is no longer increasing exponentially, suggesting that at least in the short term, the epidemic may have peaked. By September, six vCJD cases had been reported in France, and single cases in Ireland, Italy, Canada and the USA. The vCJD cases reported in France and Italy did not have a history of residence in the UK but the cases reported in Ireland, Canada and the USA had a history of UK residence during the late 1980s. SEAC welcomed the evidence of a decline in the epidemic but expressed caution as it considered that future peaks in the epidemic could not be discounted.

First probable case of blood transfusion associated transmission of vCJD

17. In February, SEAC was updated about the Transfusion Medicine Epidemiology Review (TMER) funded by the Department of Health (DH) to examine possible links between vCJD and blood transfusion. In the course of the study, a case of possible transmission of vCJD by blood transfusion had been identified. The recipient received blood in 1996 from a donor who, at the time of donation, was free of clinical signs of vCJD, although went on to develop vCJD in 1999. The blood recipient died of vCJD in 2003. Although the possibility could not be ruled out that the blood recipient was infected as a consequence of consuming meat products contaminated with the BSE agent, statistical analysis suggested that it was unlikely that the association between the blood recipient and the blood donor was due to chance.

18. SEAC agreed that the case raised the possibility that the infection may have been transmitted by the blood transfusion. However, it was

noted that this was a single case. The recipient had received blood before leucodepletion of blood donations had been adopted in the UK in 1998, as a precautionary measure. The measure was introduced as it was considered that leucodepletion of blood would significantly reduce the risk of blood transfusion associated transmission of vCJD. SEAC noted the importance of the TMER in identifying potential transfusion associated vCJD cases.

CJD surveillance in Switzerland

19. In February, SEAC was informed about the epidemiology of sporadic CJD (sCJD) in Switzerland. In recent years, an increased incidence of sCJD had been noted that could not be linked to patient gender, age, geographical location, surgery or occupation. In common with other countries, the increased incidence had been noted following the introduction of testing for the protein marker 14-3-3 as an aid to differential diagnosis of sCJD. The committee agreed with the Swiss investigators that improved surveillance and an increased awareness of the disease rather than a real rise in the number of cases may explain the rise in disease incidence. An analysis of Western Blot profiles of the cases was inconsistent with a diagnosis of vCJD. However, strain typing bioassays of tissues collected from the cases together with material collected from vCJD cases and animals with BSE, scrapie or chronic wasting disease were planned to confirm the diagnosis of sCJD. The committee agreed that strain typing experiments were important and that incubation times and lesion profiles would be likely to provide a clearer distinction between different prion disease strains compared with Western Blot profiles.

Survey of human tonsil and appendix samples

20. In February, SEAC considered the results from an unlinked and anonymised retrospective survey of human appendix and tonsil samples. This was funded by DH, to determine the prevalence of detectable abnormal PrP in these tissues. Of 12 674 samples tested, detectable levels of abnormal PrP were found in three appendix samples. One sample showed an immunohistochemical staining pattern similar to that observed with vCJD cases. In the other two samples, the immunostaining was dissimilar to that typically observed with vCJD cases. The committee considered it was possible that the atypical immunostaining could be an experimental artefact. Alternatively, it could represent infection at an early stage of the incubation period or signify the existence of a carrier state or different

infection phenotype possibly with a longer incubation period than had been observed with the vCJD cases reported to date.

21. Assuming all three positive samples represented real infections, the data indicated that the estimated prevalence of vCJD could be around 237 infections per million of the population (95% confidence interval 49-692 per million). If it was assumed that this prevalence related to people aged 10-30 years (83% of the samples were from people within this age range) then around 3800 individuals (95% confidence interval 785-11128) aged 10-30 years could be infected with vCJD in the UK. The committee noted that this prevalence of infection with the vCJD agent was appreciably higher than that predicted from the number of vCJD cases recorded to date. To date all of the clinical cases of vCJD have been the same PrP genotype (PrP codon 129 methionine homozygotes). However, it is possible that other PrP genotypes may also be infected but develop the disease after a longer incubation period.

22. The committee was also informed about an unlinked and anonymised prospective survey of tonsil samples. In this study, samples would be collected and analysed in batches of 5000 until approximately 100 000 had been collected in total. The committee endorsed the decision to batch analyse samples and recommended that ethical approval be obtained to allow the PrP genotype of positive samples to be determined.

Bone risk assessment

23. In February, SEAC considered an updated risk assessment, produced by the National Blood Service (NBS) and DH to examine the risk of transmission of vCJD via implantation of human bone. The assessment compared the risks associated with different bone products (processed or unprocessed, pooled or unpooled) under different scenarios of infectivity. The risk assessment showed that the theoretical risk of transmission of vCJD via bone transplantation is increased by pooling, because of the possibility of sourcing infectious material from any one of multiple donors. Processing of bone reduced the amount of blood and marrow, lowering the risk of infection.

24. The committee agreed with the general approach used in the risk assessment, noting that the risk of infection would also depend on the prevalence of vCJD in the general population. The committee concluded that the use of unpooled bone, and removal of blood and

marrow from bone, minimises the risk of vCJD transmission via the implantation of human bone.

Tissue risk assessment

25. In February, SEAC considered a draft risk assessment of vCJD transmission via tissue transplantation, produced by NBS and DH to identify critical procedures to minimise the potential for transmission. The assessment indicated that factors affecting the level of risk of infection by transplantation included the type of tissue, pooling of tissues, mass of tissue transplanted, age of donor and recipient and the site of transplant. A lack of scientific data on the potential levels of infectivity in different tissues precluded the production of a quantitative risk assessment.

26. The committee agreed that the scientific uncertainty relating to tissue infectivity meant that it was difficult to conduct a quantitative risk assessment but concluded that the approach adopted in the assessment was reasonable. Systems, such as the TMER to trace the use of human tissues in medical procedures, were considered to be an important surveillance mechanism to identify iatrogenic transmission of vCJD.

Second probable case of blood transfusion associated transmission of the vCJD agent

27. In June, DH asked the committee to advise on the public health implications of a second probable case of blood transfusion associated transmission of the vCJD agent. The patient who died in 2004, from a cause unrelated to vCJD, showing no clinical signs of vCJD, had received a single unit of blood in 1999. This blood was donated by an individual who subsequently developed vCJD in 2000 and died in 2001. Post mortem findings in the blood transfusion recipient suggested a possible preclinical case of iatrogenic vCJD associated with blood transfusion. However, the patient resided in the UK, and oral exposure to the BSE infectious agent could not be excluded as a possible cause of infection.

28. On the basis of a statistical analysis of the possible causes of infection, the committee agreed that the case was much more likely to be attributable to blood transfusion, than food borne infection. The report strengthened the evidence for the transmission of vCJD via blood. However, the committee noted that in this instance, although vCJD infection appeared to have been transmitted, it was not known if clinical vCJD would have developed if the patient had lived longer.

29. The committee agreed that the new case strengthened its opinion, first stated in October 1997, that human blood from persons incubating vCJD may be infective. Additionally, it was a public health priority for all recipients of blood transfusions from donors incubating vCJD to be subject to post mortem investigation, to help quantify the nature and magnitude of the risks of transmission of vCJD via blood. A statement summarising the committee's consideration of the case is given at Annex 7.

Transmission of vCJD via surgical instruments

30. In September, SEAC considered an updated risk assessment by DH on the transmission of vCJD via surgical instruments. This assessment examined the consequences of an operation on an infected patient, in terms of the number of subsequent infections that could possibly arise from use of potentially contaminated instruments. The implications of such infections for the spread of vCJD in the UK population were modelled. The assessment identified key variables that influenced the risks. Due to the paucity of data, particularly on tissue infectivity and the effectiveness of decontamination practices, there were multiple uncertainties in the assessment.

31. The committee was generally content with the approach taken in the risk assessment. It concluded that effective cleaning and decontamination of instruments was the most important measure to reduce the risks of transmission of vCJD via the use of surgical instruments.

Maternal transmission of vCJD

32. In November, at the request of the Chief Medical Officer for England, SEAC considered current evidence on the potential transmission of vCJD from mother to child, via human breast milk. *In utero* transmission was also considered. The committee considered the limited published epidemiological and experimental research on maternal transmission of prion diseases, together with unpublished surveillance data of children born to vCJD cases from the National CJD Surveillance Unit and the PIND surveillance of neurological illness in UK children[1]. The committee also commented on a modelling work by DH on the effect of pooling breast milk in breast

[1] Devereux *et al*. (2004) Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). *Arch Dis Child*. 89, 8-12.

milk banks on the possible transmission of vCJD via the use of such milk.

33. The committee noted that the modelling clearly showed that the practice of pooling breast milk increased the potential risk because it increased the number of donors to which a recipient is exposed. This therefore increased the potential risk of an infant receiving milk contaminated with vCJD infectivity. The committee concluded that the theoretical risk of infection could be minimised by not pooling the milk, by the use of individual hand operated breast milk pumps for single donors, and by the use of single use sterilised bottles for collection. As the available evidence suggested that infection/inflammation of the breast results in increased lymphocytes in milk, therefore increasing the risk of infectivity, risk would be minimised if milk from donors showing signs of infection was not used. The committee suggested that, if practicable, milk might be stored for an appropriate period of time to allow the health status of donors to be monitored, before it is released.

34. The committee concluded that there was no epidemiological evidence for maternal transmission of vCJD, including transmission via breast milk, however a hypothetical risk exists. Although evidence was limited and mostly indirect rather than direct, the risk, if any, appeared to be low. However, a watching brief should be maintained. The committee recommended that undiagnosed neurological diseases be carefully monitored and monitoring of neurological illnesses, such as the PIND surveillance of children, continue. A position statement summarising the committee's consideration is given at Annex 8.

B. Food Safety and the Protection of Animal Health

American BSE case

35. In February, SEAC was informed that a case of BSE had been identified in an animal in the United States of America (USA). UK imports of beef from third countries are strictly controlled and very little US beef was imported because of other trade restrictions. SEAC asked to be kept up to date on the USA surveillance programme for BSE.

Survey of historic butchery practices

36. In April, SEAC considered the results of a survey of historic butchery practices in Great Britain (GB), undertaken by DNV Consulting on

behalf of the FSA. The survey was commissioned following a report of an investigation by the Leicestershire Health Authority (LHA) into a cluster of vCJD cases in the village of Queniborough. This suggested that local butchery practices may have resulted in a risk of cross-contamination of beef carcass meat with bovine brain.

37. The survey determined the prevalence of the butchery practices as identified in the LHA report, and the extent of change in practices over time. The survey assessed the impact of any legislative changes made to farming and abattoir practices during the time period under investigation (1980-1995). It also considered other factors related to butchery practices that may have affected exposure to BSE infectivity.

38. The survey showed that the butchery practices in the LHA were not significantly different from the rest of GB. The survey confirmed that, during that time period brain matter had entered the human food chain. However, there had been no observed increase in vCJD cases in those groups of people (older persons) thought to have had the highest consumption of this material.

39. The committee concluded that although the study provided some useful insights into the butchery practices carried out at the height of the BSE epidemic, it did not provide any additional information about the route of BSE infection in humans.

Report from FSA/SEAC risk assessment group

40. In April, the FSA asked the committee to comment on the conclusions reached by the FSA/SEAC Risk Assessment Group (RAG). RAG had been convened to provide scientific advice to the FSA on the levels of risk to the consumer from changes to the Over Thirty Month Rule (OTMR)[2]. Earlier in April, RAG had considered the impact of replacement of the OTMR with BSE testing of cattle over 30 months of age, taking into account new scientific data on a case of vCJD thought to be acquired by blood transfusion and the results of a retrospective survey of human tonsil and appendix tissue. SEAC members expressed a spectrum of views as to how the survey data and vCJD case data should be incorporated into the risk assessment. Both SEAC and RAG agreed that the new data did not fundamentally change the underlying assumptions in the risk assessment and that replacing the OTMR with testing cattle would result in only a very small increase in the estimated potential overall size of the vCJD

2 The OTMR is the BSE control initiated in 1996 that bans all animals (including imported carcasses) over 30 months from entering the human food supply in the UK.

epidemic. A statement summarising the RAG and SEAC consideration is given at Annex 9.

OTMR review risk assessment

41. In June, SEAC was asked by the Food Standards Agency (FSA) to consider further modelling work by Imperial College London that compared the risks of different changes to the OTMR. Options for changes included allowing only healthy or a combination of healthy and casualty animals over thirty months old into the food chain, subject to the EU BSE testing requirements. This analysis utilised the estimates of the human exposure to BSE previously considered by SEAC, and an integrated estimate of the size of the vCJD epidemic based on the case data and the new data from the retrospective tonsil/appendix study[3]. The modelling showed that removal of the OTMR would result in very small numbers of future vCJD cases, relative to the size of the overall epidemic.

42. The committee was content with the approaches used and noted that pessimistic assumptions had been incorporated in the modelling work. These included assumptions that the future BSE infection risk for cattle would remain constant at the level in 1999, the low sensitivity of TSE diagnostic tests prior to the onset of clinical disease and the similar susceptibility of all human PrP genotypes to infection. The committee also noted that the inclusion of casualty animals increased the level of risk disproportionately to the number of casualty animals entering the food supply. Therefore it was recommended that the FSA Board note this when considering risk management options for changes to the OTMR. A statement summarising the assessment of the future number of vCJD cases arising from relaxation of the OTM scheme is given at Annex 10.

BSE update

43. In September, SEAC was updated on the number of BSE infected cattle in the UK, and worldwide, since 1988. In GB, the BSE epidemic had peaked in 1992, when over 36500 cases were confirmed, but thereafter the number of cases had declined considerably. In GB to date, around 183000 BSE cases had been recorded. BSE had also been reported within, and in countries outside, the European Union (EU).

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

44. Following an EU requirement, an active surveillance programme had been in place since July 2001. The combined BSE cases identified by passive and active surveillance from January 1999 to August 2004 had also shown a sharp decline. The decline indicated that the reinforced feed ban introduced in 1996 had substantially reduced the risk of feed-born infection. Despite this a total of 97 BARB cases (BSE cases Born After the Reinforced Ban) had been identified in the UK, 84 in GB and 13 in Northern Ireland as at 28th September 2004. The committee noted that research was underway to investigate the origin of these cases.

45. It was noted that there were cases of animals with clinical signs consistent with BSE, that were not confirmed as BSE cases, using the diagnostic tests applied. The committee considered that research on methods to allow differential diagnosis of clinical cases of BSE was important particularly in view of evidence on the phenotypic differences in infection in humans and sheep.

FSA contingency policy for possible BSE in sheep

46. In September, SEAC was asked to advise on the underlying scientific assumptions and approaches adopted in two modelling studies carried out by the Veterinary Laboratory Agency (VLA) / Institute of Animal Health and the University of Oxford for the FSA. These would inform its contingency policy should BSE ever be found in sheep. The modelling studies, based upon discriminatory testing of almost 2400 samples from scrapie suspects by the VLA together with published and unpublished data on the pathogenesis of BSE and scrapie in sheep, examined the possible prevalence of BSE in sheep and the likely impact of different risk reduction strategies if BSE was found in sheep. The committee also considered the analytical methods used to discriminate BSE and scrapie in sheep.

47. The committee considered that tests to distinguish BSE from scrapie had limitations but were becoming more robust. Studies to date showed no evidence for BSE in UK sheep. The committee acknowledged the theoretical nature of the modelling work and that modelling the possible impact of BSE in sheep if it entered the national flock was complex. Due to the very limited data available, the models had necessarily relied heavily on many assumptions. In particular, the modelling assumed that BSE and scrapie would behave similarly in all types of sheep, which is largely unknown. The committee noted that the modelling indicated that a single BSE infected sheep entering the food supply could present a significantly

greater risk compared to the current risk from a single infected bovine. They also noted that the model suggests that a risk reduction strategy based on the PrP genotype of sheep would be the most effective, if BSE were found in the national flock. A summary of the committee's consideration that was provided to the FSA is given at Annex 11.

Chronic wasting disease in UK deer

48. In November, SEAC was asked by the FSA to consider the possible public health implications of chronic wasting disease (CWD). CWD is an endemic TSE in certain captive and free-ranging species of deer in some areas of North America. It has not been found in the UK, or elsewhere in Europe. The committee also considered the possibility that BSE may also be present in UK deer.

49. The committee concluded that there is no evidence of CWD (or BSE) in the UK deer population. However, because limited surveillance is conducted, a low level prevalence of CWD could not be ruled out. Further surveillance of TSEs in UK deer was recommended. The committee considered that there was no evidence of transmission of CWD to humans from consumption of meat from infected deer (or to cattle, sheep or goats by natural means), although the data are limited. Thus, the committee concluded that CWD currently poses relatively little risk to human health but a watching brief should be maintained. A position statement summarising the committee's consideration is given at Annex 12.

C. Safety of Animal By-Products

Uses of collagen from hides of UK cattle

50. In April, Defra asked SEAC to comment on the safety of sourcing collagen from the hides of UK cattle[4]. A UK Regulation imposed in 1999[5] prohibited the production of collagen from UK cattle hides for such uses. However, as insufficient quantities of hides could be sourced from other EU countries, a UK based company producing collagen had submitted a request to Defra to recommence sourcing of collagen from the hides of UK cattle.

4 Collagen is a family of fibrous proteins found in connective tissues such as the hides, bones, tendons and cartilage. It is used for a number of purposes, e.g. sausage casings, cosmetics, and in vascular surgery, corneal shields, wound dressings, hard tissue repair, bulking agents for incontinence. It is also used in drug delivery.

5 The Bovine and Bovine Products (Trade) Regulations 1999, prohibit the production of collagen from UK bovine hides to ensure compliance with the UK export ban on beef and beef products.

51. The committee was informed that research to date had not detected infectivity in cattle hides. The World Health Organisation had classified bovine hides as a tissue with no evidence of BSE infectivity. Therefore, if infected animals were slaughtered the most likely route of infectivity would be due to contamination with brain tissue at slaughter. However as the whole head including the hide is classified as specified risk material (SRM) in the UK, the risk of cross contamination in the UK would be less than in other EU countries where the head hide may be used.

52. The committee considered the potential risk from using UK collagen for food would be minimal if the collagen could be sourced from the hides of animals fit for human consumption. In considering the implications for use of UK derived collagen in pharmaceutical and medical products, SEAC asked for additional information on the regulations governing end-use of collagen in these products. In addition, the committee considered it would require information on the prevalence of BSE in the UK and other European countries before it could consider the relative risk of sourcing European versus UK derived bovine material for such purposes. In considering relative risk it would be important to consider the UK position both pre- and post-changes to the OTMR.

Effects of tallow separation on abnormal prion protein

53. In June, SEAC was updated on the findings of an experimental study by the Veterinary Laboratories Agency (VLA) on the effect of the rendering process on TSE infectivity, and the distribution of abnormal PrP. After slaughter for human consumption, by-products from animal carcases are cooked and the molten fat fraction (tallow) separated from the protein-rich solid portion (greaves). The greaves are pulverised to produce meat and bone meal (MBM). Historically, solvents were used to extract further tallow from the greaves, but this had been phased out in the decade prior to the BSE outbreak. It had been suggested that the solvent extraction of tallow from the greaves had previously protected the cattle food chain by either inactivating the BSE agent during the solvent and/or steam treatment, or by partitioning the agent into the tallow and thus removing it from the MBM.

54. In the study, infectivity levels in samples from all stages of the rendering process had been measured by mouse bioassay. Varying levels of infectivity had been detected in the raw and rendered greaves, and in tallow fractions. The committee concluded that the

data from the study, although incomplete, did not support the hypothesis that cessation of solvent extraction of greaves may have led to increased available infectivity in MBM and the start of the BSE epidemic.

D. Research on TSEs

Atypical BSE cases

55. In February, SEAC considered the findings of a research paper (Casalone *et al.* 2004)[6] suggesting that a second bovine amyloidotic spongiform encephalopathy had been identified with a molecular signature similar to that of a subtype of sCJD. The committee agreed that the results were very interesting, but without information on the transmissibility of the disease in bioassays, it was premature at this stage to conclude it was a new strain of BSE. SEAC agreed it would follow further research on these samples with interest.

DH research update

56. In February, SEAC was updated on DH funded research including work on the diagnosis of CJD, the safety of blood and blood products, the detection of abnormal PrP, the decontamination of surgical instruments and potential treatments for vCJD. The committee noted that progress had been made on both detection and inactivation of prions on surgical instruments. However, a pre-clinical test for vCJD had not yet been developed. Several research programmes on potential vCJD therapies were underway and a clinical trial protocol had been developed for potential drugs.

Research on prion propagation in yeast

57. In April, SEAC reviewed papers by King & Diaz-Avalos (2004)[7] and Tanaka *et al*. (2004)[8]. These showed that, in yeast, PrP could adopt different conformations to form transmissible particles that propagate different prion strains, independently of nucleic acid. The committee considered that the findings provided a proof of principle for the prion hypothesis, whereby prions can change conformation into self-

6 Casalone *et al.* (2004) Identification of a second bovine amyloidotic spongiform encephalopathy: molecular similarities with sporadic Creutzfeldt-Jakob disease. Proc. Natl. Acad. Sci. USA 101, 3065-70.

7 King & Diaz-Avalos (2004) Protein-only transmission of three yeast prion strains. Nature. 428, 319-23.

8 Tanaka *et al*. (2004) Conformational variations in an infectious protein determine prion strain differences. Nature. 428, 323-8.

propagating forms, without the need for nucleic acid. However, caution was expressed about extrapolating the findings in yeast to the pathogenesis of prion diseases in mammals.

Termination of cattle bioassays

58. In November, SEAC was informed that FSA-funded cattle bioassays to define the pathogenesis of BSE in cattle would be terminated. This was on grounds of animal welfare and to focus funding on research to develop non-invasive live animal diagnostic tests. The cattle used for the initial bioassays were reaching eight years post inoculation. An analysis had shown that termination of the studies at approximately seven years post inoculation would not result in any measurable loss of data. Thus, once each of the challenge groups reached seven years, the animals would be culled and a series of tissues archived. The committee was content with the scientific rationale for termination of the cattle bioassays but stressed the importance of archiving appropriate tissues to allow for further study of these samples in the future, if required.

E. TSEs in sheep

Report from CRL expert group on strain typing

59. In April, SEAC were informed about the work of the Community Reference Laboratory (CRL) expert group. This group was established to investigate the possible presence of BSE in sheep, and to coordinate a ring-trial of TSE positive samples from sheep and goats using tests that could potentially discriminate between BSE and scrapie. It had been found that the tests were able to consistently discriminate between BSE and scrapie, but differences in test sensitivity were evident when samples from different regions of the brain were tested. On the basis of these results, the CRL expert group had provisionally agreed a classification for reporting results to national reference laboratories.

60. In the course of this work one sample from a UK TSE infected sheep did not appear to resemble previously recognised cases of scrapie in Western Blot tests. Although there were some differences, some characteristics of the sample were similar to experimental BSE in sheep, and an experimental strain of sheep scrapie. When tested using immunohistochemistry, the sample was interpreted as being ‘scrapie-like’. The CRL expert group proposed to further investigate this sample with bioassays. The committee agreed with the

conclusions of the CRL expert group that this case could not be categorised as 'BSE in sheep'.

Sheep subgroup

61. In March, Defra consulted the SEAC sheep subgroup following reports that abnormal PrP had been detected in the brains of ARR/ARR sheep, a PrP genotype thought to be naturally resistant to scrapie. The subgroup was asked to consider if this development had any implications for the scientific basis of the National Scrapie Plan (NSP). The sheep subgroup endorsed their previous opinion of December 2002, that the NSP strategy to increase resistant genotypes and decrease susceptible genotypes remained scientifically justified. It considered that, although the new evidence suggested that the ARR/ARR genotype may not be completely protective against natural TSE infection, the relative protection, compared to other genotypes, remained very large. However, the basis for the strategy should be kept under review in the light of emerging scientific findings with respect to the possible detection of scrapie infections in animals of genotypes currently thought to be most resistant to infection.

62. In July, the SEAC sheep subgroup considered four options proposed by Defra for the NSP as part of a wider consultation of stakeholders on future plans for the NSP. In its consideration of the options, the subgroup was of the view that strategies, which reduced the prevalence of infection in the national flock most rapidly, were the most desirable. The subgroup considered a solution close to the current NSP, with compulsory ram genotyping and removal from use and sale of some scrapie-susceptible genotypes, was the most scientifically desirable. However, it recognised that there may be potential practical difficulties with this option. In some cases there were genetic constraints for the sheep industry as well as associated cost issues and therefore the subgroup recommended that an additional option, a combination of mandatory and voluntary genotyping of certain sheep with removal of some genotypes could also be considered. An explanation of the options for the NSP and a statement from the SEAC sheep subgroup on the options is given at Annex 13.

63. In September, SEAC endorsed the sheep subgroup's statement.

Recommendations

64. In the course of the year the committee provided the following advice to Government:

- removal of blood and marrow from bone and use of unpooled bone minimises the risk of vCJD transmission via medical procedures involving implantation of human bone (paragraph 24),

- all blood transfusion recipients from donors incubating vCJD should be subject to post mortem investigation, to help quantify the nature and magnitude of the risks of transmission of the vCJD agent through blood (paragraph 29),

- effective cleaning and decontamination of surgical instruments is the most important measure to reduce the risks of possible transmission of vCJD, via the use of surgical instruments (paragraph 31),

- the theoretical risk of infection via breast milk banks could be minimised by not pooling milk, by the use of individual hand operated breast milk pumps for single donors and by the use of single use sterilised bottles for collection. Additionally, risk would be minimised if milk from donors showing signs of infection was not used and, if practicable, milk could be stored for an appropriate period of time to allow the health status of donors to be monitored, before it is released (paragraph 33),

- inclusion of casualty animals increased the level of risk disproportionately to the number of casualty animals entering the food supply and that this should be noted when assessing risk management options for changes to the OTMR. (paragraph 42),

- that the modelling presented to the committee suggests that a risk reduction strategy, based on PrP genotype of sheep, would be the most effective if BSE were found in the national sheep flock (paragraph 47),

- the NSP strategy remains appropriate but should be kept under review in the light of emerging scientific findings with respect to the possible detection of scrapie infections in animals of

genotypes currently thought to be most resistant to infection (paragraph 61),

- the NSP strategy of compulsory ram genotyping scheme with removal from use and sale of some scrapie-susceptible genotypes is the most scientifically desirable but a combination of mandatory and voluntary genotyping of certain sheep could also be considered (paragraph 62).

65. The committee also made the following recommendations in relation to research and surveillance:

- systems such as the TMER to trace the use of human tissues in medical procedures are an important surveillance mechanism tool for identifying iatrogenic transmission of vCJD (paragraph 18),

- ethical approval be obtained to allow the PrP genotype of positive samples to be determined in the survey of abnormal PrP in tonsil samples (paragraph 22),

- undiagnosed neurological diseases should be carefully monitored, and monitoring of neurological illnesses, such as the PIND surveillance of children, should continue (paragraph 34),

- research on methods to allow differential diagnosis of clinical cases of BSE is important in view of evidence on the phenotypic differences in infection in humans and sheep (paragraph 45),

- further surveillance of TSEs in UK deer should be conducted (paragraph 49),

- when terminating cattle bioassays tissues should be archived to allow for further study of these samples in the future, if required (paragraph 58).

Annex 1

Abbreviations

BARB	Born After the Reinforced Ban cases
BSE	Bovine Spongiform Encephalopathy
CJD	Creutzfeldt Jakob Disease
CRL	Central Reference Laboratory
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
EU	European Union
FSA	Food Standards Agency
GB	Great Britain
MBM	Meat and Bone Meal
NBS	National Blood Service
NSP	National Scrapie Plan
OTM	Over Thirty Month
OTMR	Over Thirty Month Rule
RAG	FSA/SEAC Risk Assessment Group
SEAC	Spongiform Encephalopathy Advisory Committee
sCJD	Sporadic Creutzfeldt-Jakob Disease
SRM	Specified Risk Material
TMER	Transfusion Medicine Epidemiology Review
TSE	Transmissible Spongiform Encephalopathy
USA	United States of America
vCJD	variant Creutzfeldt-Jakob Disease
VLA	Veterinary Laboratory Agency

Annex 2

Membership of the Committee

Professor Chris Higgins

SEAC Chair. Director of the MRC Clinical Sciences Centre and Head of Division at Imperial College London.

Mr John Bassett

Risk assessor, specialising in microbiology, at the Unilever Safety and Environmental Assurance Centre.

Dr David Brown

Lecturer in the Department of Biology and Biochemistry at the University of Bath.

Mr Colin Browne

Partner in the Maitland Consultancy, which provides advice to corporate organisations on external communications.

Professor Graham Bulfield

Vice-Principal and Head of the College of Science and Engineering at the University of Edinburgh.

Dr Jacky Chambers

Director of Public Health, Heart of Birmingham Teaching Primary Care Trust and Birmingham City Council.

Professor Nigel Hooper

Professor of Biochemistry at the School of Biochemistry and Microbiology, University of Leeds.

Professor James Ironside

SEAC Deputy Chair. Professor of Clinical Neuropathology in the University of Edinburgh and Director of the National CJD Surveillance Unit, Edinburgh.

Mr Peter Jinman

Private Veterinary Surgeon and member of the Royal College of Veterinary Surgeons.

Dr Corinne Lasmezas

Head of the prion research group at the Service de Neurovirologie (SNV), France.

Professor Jean Manson

Head of TSE division and Neuropathogenesis Unit at the Institute for Animal Health.

Professor Ian McConnell

Professor of Veterinary Science at the University of Cambridge and Director of Research at the University of Cambridge Veterinary School.

Ms Diane McCrea

Independent consultant on food and consumer affairs.

Professor Graham Medley

Head of the Ecology and Epidemiology Research Group in the Department of Biological Sciences at the University of Warwick.

Dr Peter Rudge

Consultant neurologist at the National Hospital for Neurology and Neurosurgery and is physician attached to the CJD cerebral biopsy committee.

Professor Margaret Stanley

Professor in Epithelial Biology in the Department of Pathology, University of Cambridge.

Members who left the committee during the year:

Professor Peter G. Smith

Outgoing SEAC Chairman. Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine.

Professor Adriano Aguzzi

Head of the Institute of Neuropathology, University of Zurich, Director of the Swiss Reference Centre for Prion Diseases and Associate Dean for Research Zurich Medical School, Switzerland.

Professor Christopher Bostock

Consultant on TSE Research.

Professor Robin Carrell

Professor of Haematology at the University of Cambridge

Professor Harriet Kimbell

Associate Professor at the Guildford College of Law. Further details on each of the current SEAC Members may be found on the SEAC Website: http://www.seac.gov.uk/membership.htm

Secretariat

Dr Catherine Boyle (Secretary until November 2004)

Ms Kate Richards (Secretary from November 2004)

Dr Tom Barlow (from September 2004)

Ms Tabitha Dale

Dr Brett Jeffrey (until August 2004)

Dr Pat Keep

Mr Martin Pemberton

Dr Chelliah Ravi Rajan

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Annex 3

Indemnity by the Minister for Environment, Food and Rural Affairs and the Secretary of State for Health, to members of the Spongiform Encephalopathy Advisory Committee and Related Committees

1. The Minister and the Secretary of State ("the Ministers") hereby jointly undertake with each of the members of the Spongiform Encephalopathy Advisory Committee and all of its sub-groups covered by the code of practice ("the members") that they will indemnify them, their estates and their heirs against all personal civil liabilities in respect of any action or claim which may be brought, or threatened to be brought, against them either individually or collectively by reason of or in connection with the performance at any time of their duties as members, whether before or after the date of this indemnity, including all costs, charges and expenses which the members or any member may properly and reasonably suffer or incur in disputing any such action or claim.

2. The members or any member shall as soon as reasonably practicable notify the Ministers if any action or claim is brought or threatened to be brought against them or any of them in respect of which indemnity may be sought pursuant to paragraph 1. If any action or claim is brought the Ministers shall be entitled to assume the defence. The Ministers shall notify the members or member as soon as practicable if the Ministers intend to assume the defence and the members or member shall then provide such information as the Ministers reasonably request, subject to the Ministers reimbursing all out of pocket expenses properly and reasonably incurred by members or any of them. The Ministers shall, where reasonable and practicable, consult with and keep the members or any of them informed of the progress of the action or claim. Where Ministers do not assume the defence, members or any of them shall keep the Ministers fully informed on its progress and any consequent legal proceedings and consult with the Ministers as and when reasonably required by them or any of them concerning the action or claim.

3. The indemnity contained in paragraph 1 shall not extend to any losses, claims, damages, costs, charges, expenses or any other liabilities:

a) in respect of which members are indemnified by or through any defence organisation or insurers; or

b) which may result from bad faith or wilful default or recklessness on the part of the members; or

c) which may result from any of the following circumstances (without the prior written consent of the Ministers having been obtained such consent not to be unreasonably withheld):

- any settlement made or compromise effected of any action or claim brought, or threatened to be brought, against them; or

- any admission by the members of any liability or responsibility in respect of any action or claim brought, or threatened to be brought, against them; or

- members taking action that they were aware, or ought reasonably to have been aware, might prejudice the successful defence of any action or claim, once the members had become aware that such an action or claim had been brought or was likely to be brought.

Signed on behalf of the Minister of Environment, Food and Rural Affairs and the Secretary of State for Health:

Signature:

Name:

Date:

Signed:

Members' name:

Date:

Annex 4

Register of Members' Interests at 31 December 2004

SEAC Member	Commercial interests		Non-commercial interests	
	Name of organisation	**Nature of interests**	**Name of organisation**	**Nature of interest**
Professor Chris Higgins	Microscience GSK	Chair SAB GSK-Imperial steering group	CR-UK MRC Imperial College Kennedy Institute for Rheumatology 2HigherGround	Programmes committee Employee. Strategy Board Head of Division Trustee Trustee
Mr John Bassett	Unilever PLC	Employee	None	
Dr David Brown	None		European Livestock Association MRC College of experts	Advisor Advisor
Mr Colin Browne	None		None	
Professor Grahame Bulfield	Edinburgh Research and Innovation Limited Scottish Institute for Enterprise B&K Universal British Biotech plc	Non-Executive Director Board Member Non-Executive Director Shareholder	University of Edinburgh Scottish Higher Education Funding Council: Research Policy Advisory Committee Genetics Society	Member of Senatus and Court Member Member

Professor Grahame Bulfield (cont.)	Viragenics Inc	Non-Executive Director	World Poultry Science Association British Cattle Breeders Club Institute of Biology Royal Society of Edinburgh Royal Agricultural Society of England Royal Society of Arts Scottish Enterprise/Royal Society of Edinburgh: Enterprise Fellowship Committee Home Office: Animal Procedures Committee Nuffield Council on Bioethics Working Party	Member Member Fellow Fellow Honorary Fellow Fellow Member Member Member
Dr Jacky Chambers	None		None	
Professor Nigel Hooper			GlaxoSmithKline Medical Research Council, BBSRC, British Heart Foundation, Wellcome Trust	Research collaborations In receipt of research funding
Professor James Ironside	Millenium Pharmaceuticals	Consultancy	Department of Health and Scottish Executive	Funding of National CJD Surveillance Unit (NCJDSU)

Professor James Ironside (cont.)	Baxter	Funding for experimental transmission studies (non-personal)	Department of Health Department of Health European Commission	Funding of NCJDSU Brain and tissue Bank Grant support for research Grant support for research (TSELAB and Neuroprion)
Mr Peter Jinman	Laurels Veterinary Group	Private Veterinary Practice	British Veterinary Association BBC Rural Affairs Committee Defra, Medical Research Council, BBSRC, Department of Health and European Commission	Past President Member of Rural Affairs Advisory Committee Grant support for research
Dr Corinne Lasmezas	LFB Ferring	Member SAB Member SAB	European Commission EMEA (EU) Defra AFSSAPS (FR) INRA (FR)	EU funded research projects CPMP member Advisor Advisor Member SAB
Dr Jean Manson	Genomia Management Ltd	Director	None	
Professor Ian McConnell	None		Wellcome Trust DEFRA BBSRC	Research support
Ms Diane McCrea	None		Institute of Food Research, Norwich University of Reading p/t post	Member of Governing Body Research support to EU funded project

Ms Diane McCrea (cont…)			Subcontractor Advisory Committee on Animal Feedingstuffs (FSA) Advisory Committee on Research (FSA) Advisory Committee on Pesticides (PSD)	Various EU funded research projects Various small consultancy projects with consumer organisations Member Member Member
Professor Graham Medley	None		None	
Dr Peter Rudge	None		None	
Professor Margaret Stanley	CRTT Ltd Aventis PasteurMSD GSK Stevenage	Director Ad Hoc consultant Consultant	None	

Annex 5

Membership and terms of reference for the SEAC/FSA Risk Assessment Group

Membership

Professor Peter Smith (Chair)
SEAC

Dr Ray Bradley

Professor Sir John Krebs
FSA

Dr Roy Anderson
University of London

Mr Peter Jinman
SEAC member

Dr Bryan Grenfell
University of Cambridge

Dr Mark Woolhouse
University of Edinburgh

Dr Phil Minor
National Institute for Biological Standards and Control

Dr Dagmar Heim
Swiss CVO's office

Dr Graham Medley
University of Warwick

Professor Simon Cousens
London School of Hygiene and Tropical Medicine

Dr Gérard Pascal
Scientific Steering Committee

Terms of reference

To assist SEAC in advising the Food Standards Agency on the

- predicted course of the BSE epidemic in UK cattle from 2002 taking into account the results of testing;
- extent of BSE in cattle over thirty months of age now and in the future;
- level of BSE infectivity entering the food chain now and in the future continuing with the current controls;
- levels of BSE infectivity which might enter the food chain now and in the future in moving to the controls prescribed in the EU legislation including testing;

taking into account the impact of the animal feed controls, cattle identification, TSE tests and other measures since March 1996.

Annex 6

Membership of the SEAC Sheep Subgroup

Professor Peter Smith (Chair)
SEAC

Professor Chris Bostock
SEAC

Professor Robin Carrell
SEAC

Professor Neil Ferguson
Imperial College London

Dr Wilfred Goldman
Institute of Animal Health

Dr Fiona Houston
Institute of Animal Health

Dr Nora Hunter
Institute of Animal Health

Mr Peter Jinman
SEAC

Professor Ian McConnell
SEAC

Dr Jean Manson
SEAC

Annex 7

Summary of Discussion on the Second Presumed Case of Blood Transfusion-Associated Infection with vCJD

Background

1. The Department of Health sought advice from the committee on a presumed second instance of blood transfusion-associated transmission of the variant Creutzfeldt-Jakob disease (vCJD) agent. The first case of probable blood transfusion-associated transmission of vCJD[9] was considered by SEAC in February 2004.

2. The National CJD Surveillance Unit (NCJDSU) had investigated this second patient after death, as the patient was a known recipient of blood from a donor incubating vCJD. Patient confidentiality and medico-legal issues surrounding the patient at the time of reporting required that the issue was considered in the reserved session of the meeting.

3. The elderly patient died in 2004, showed no clinical signs of vCJD at the time of death, which was from an unrelated cause. The patient had received a single unit of non-leucodepleted blood in 1999 that had been donated by an individual who was confirmed in 2001 as a definite vCJD case. The donor's disease onset was in 2000.

4. The NCJDSU had investigated the neuropathology, accumulation of prion protein and PrP^{res} in autopsied tissues in the case. The PRPN genotype had also been determined. The following details were reported:

    - No evidence of a spongiform encephalopathy in an examination of brain material.

    - Immunohistochemical detection of prion protein accumulation in the spleen and in a cervical lymph node. PrP^{res} was detected by high sensitivity Western Blotting in the spleen.

    - No accumulation of prion protein was detected in multiple regions of the central nervous system, tonsils, appendix, large intestine, skeletal muscle or thymus.

    - Glycotype profile of PrP^{res} in spleen was the same as has been found in clinical cases of vCJD.

[9] Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet. 2004 Feb 7;363(9407):417-21.

- Histological pattern of PrP accumulation in the spleen and the lymph node is similar to that in two appendixes reported by Hilton *et a*l (2004)[10].

- Methionine/valine heterozygosity at codon 129 of PrP gene (PRNP).

5. SEAC was informed that the findings suggested that this might be a preclinical or subclinical case of iatrogenic vCJD associated with blood transfusion. However, UK residency of the patient meant that oral exposure to the BSE agent could not be excluded as a possible cause of infection. Statistical analysis suggested it was extremely unlikely that two cases of infection with the vCJD agent would have been detected by chance in recipients of blood from pre-onset vCJD cases, even if the prevalence of prion protein accumulation in spleen tissue in the UK population was substantially larger than suggested by studies on appendix and tonsil tissue from persons without clinical vCJD.

6. The Department of Health (DH) asked SEAC to assess the data available on this case, and to advise on the implications this finding may have on the risk associated with blood, and on any additional concerns for public health.

Summary of SEAC's discussion

7. SEAC agreed that the Western Blot results and glycotype profile suggested it was unlikely that the infection was preclinical sporadic CJD (sCJD). The committee noted that a single study by Glatzel *et al* (2003) had reported PrP^{res} in the spleen of sCJD clinical cases. However, the levels of PrP^{res} present in sCJD cases were low and detected in patients with a lengthy clinical illness from sporadic CJD.

8. The committee agreed that the statistical analysis suggested that the presence of PrP^{res} in the case was attributable to a vCJD infection acquired via blood transfusion rather than a primary infection resulting from a food borne exposure.

9. SEAC agreed that this second patient with apparent vCJD infection added to the evidence that the vCJD agent can be transmitted by blood. However the committee noted that in this instance, although vCJD infection appeared to have been transmitted, it was not known if clinical vCJD would have developed if the patient had lived longer.

10. SEAC agreed that this case added support to its view on the risk associated with blood transfusion. The finding was consistent with there being a substantial risk associated with receipt of non-leucodepleted blood from a donor incubating vCJD. The extent to which leucodepletion reduces that risk is not known.

11. The committee agreed that it should be a public health priority for all recipients of blood (leucodepleted or not) from donors incubating vCJD to be subject to the kind of careful post-mortem examination that had been possible in this case. This would help to quantify the nature and magnitude of the risks of transmission of the vCJD

[10] Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, Penney M, Hegazy D, Ironside JW. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. Journal of Pathology: 203 (3).733-739. Published Online: 21 May 2004

agent through blood [donated by preclinical cases of vCJD]. The committee re-iterated the continuing importance of the Transfusion Medicine Epidemiology Review (TMER) to identify vCJD cases who have been donors and the recipients of such donations.

12. SEAC noted that the detection of PrP^{res} in lymphoreticular tissues of vCJD cases and the presence of infection in the spleen of this case was compatible with the lymphoreticular system being involved in the early spread of infection before entering the CNS. SEAC agreed that the detection of prion protein in the spleen but not in the tonsil of the case has implications for the national anonymous tonsil archive. The SEAC chair agreed to refer this finding to the DH/MRC steering group overseeing the archive.

13. SEAC noted that the patient was heterozygous at codon 129 of the PRNP gene and that this was the first time infection with the vCJD agent had been reported in an individual not methionine homozygous. This indicated that genotypes other than the methionine homozygous were susceptible to infection with the vCJD agent. Uncertainties remain as to the relative susceptibility of heterozygotes to food borne (or other) infection or the possible outcomes of infection. The committee agreed that the similarities between the Western Blot band analysis and PrP^{res} glycoprofile seen in this case and in cases of vCJD who were methionine homozygous was reassuring with respect to the ability to make the diagnosis of vCJD in those of genotypes other than methionine homozygous.

14. SEAC stated that, in the interests of public health, this case demonstrates the importance of both in life and in death surveillance of recipients of blood products derived from blood donations from individuals subsequently found to be infected with the vCJD agent. The committee also noted that this case highlighted the importance of obtaining autopsies in such patients and, more generally, the committee reiterated the concern that it had expressed previously, that a mechanism was needed to increase the autopsy rate amongst the UK population to reduce the possibility that cases of vCJD were being missed.

15. SEAC emphasised the importance of the DH-funded sheep transfusion study which is designed to investigate the infectivity of different blood fractions taken from sheep experimentally infected with BSE by transfusing them into ARQ homozygous sheep. The committee noted that the two presumed human cases of blood transfusion-associated vCJD infection indicated the potential infectivity of transfused blood. However, current technology is unable to quantify the levels of infectivity in blood and a rapid diagnostic test remained a key research priority.

Annex 8

Position Statement on Maternal Transmission of vCJD

Issue

1. The Chief Medical Officer for England asked SEAC to consider current evidence and comment on the potential transmission of vCJD from mother to child via human breast milk. *In utero* transmission was also considered. The committee also commented on the scientific basis of a risk reduction measure for possible transmission of vCJD via banked breast milk.

Background

2. No diagnostic test is currently available for the detection of abnormal PrP in milk. Research is under way to develop tests to screen for the possible presence of abnormal prion protein (PrP) in milk samples from cattle experimentally infected with BSE[11]. These modified tests may also be applicable to human milk. However, it is not yet clear when/if a reliable test will be available.

3. A small number of breast milk banks in the UK supply highly vulnerable premature babies for whom no milk may be available from the mother. A model developed by the Department of Health to assess the effect of pooling breast milk from multiple donors on the possible risks of transmission of vCJD via breast milk banks was considered.

4. There is some, albeit limited, published epidemiological and experimental research on maternal transmission of prion diseases. There are also unpublished surveillance data of children born to vCJD cases from the National CJD Surveillance Unit and UK surveillance of neurological illness in children which might inform on potential risks of maternal transmission.

Breast milk banks

5. There is no evidence that vCJD infectivity has ever been transmitted through breast milk. However, a theoretical risk exists. Modelling studies clearly show that the practice of pooling breast milk increases the number of donors to which a recipient is exposed and thereby increases the potential risk of an infant receiving milk contaminated with vCJD infectivity. The theoretical risk of infection can be minimised by not pooling the milk, by the use of individual hand operated breast milk pumps for single donors, and by the use of single-use sterilised bottles for collection. In addition, available evidence suggests that infection/inflammation of the breast results in increased lymphocytes in milk and therefore increased risk of infectivity. This risk would be minimised if milk from donors showing signs of infection is not used.

[11] A joint FSA/SEAC milk working group is monitoring and providing advice on this research carried out at the Veterinary Laboratories Agency.

6. The committee suggested that, if practicable, milk could be stored for an appropriate period of time to allow the health status of donors to be monitored, before it is released. However, information was not available to the committee on whether long-term storage of human milk is detrimental to its nutritional quality.

Maternal transmission

7. There is evidence from animal studies for low level maternal transmission of prions in cattle and sheep. This transmission may occur *in utero*, via milk and/or perinatally. However, the possibility that this putative maternal transmission might have been due to another mode of transmission, for example through a contaminated environment or feed, cannot be ruled out.

8. In contrast, in humans there is no evidence for maternal transmission in cases of familial prion disease, other than the transfer of a mutant form of the PrP gene, and there is no evidence of maternal transmission of Kuru. However, compared with other human prion diseases vCJD may pose a greater risk because of the greater involvement of the lymphoreticular system in vCJD pathogenesis. Although, breast tissue (and placenta) from a single vCJD case tested negative for PrP^{vCJD}, transfer of infectivity to breast milk may depend on the physiological status of the mammary gland. Similar tests or infectivity bioassays have not been conducted on breast tissue from lactating patients with vCJD.

9. A published study suggesting transmission of sCJD in colostrum[12] was considered unreliable because tissues not normally associated with high levels of infectivity (blood and placenta) showed equivalent infectivity to that of the brain in this study.

10. Analysis of prospective surveillance data of UK children born to mothers with, or that had subsequently developed clinical vCJD, provide no evidence for maternal transmission of vCJD. However, the number of cases is very small and the incubation period of vCJD, if transmitted from mother to child, is unknown and so the children may yet be too young to have developed symptoms.

11. The phenotype of BSE infection in humans expressing PrP genotypes other than M/M at codon 129 is not known. Given recently published studies in mice expressing the human PrP gene[13], which suggest that the human PrP genotype may affect disease phenotype, the committee considered it very important that undiagnosed neurological diseases be carefully monitored. In this respect, amongst others, it is recommended that the careful monitoring of neurological illnesses through the PIND surveillance of children[14] continue.

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[12] Tamai Y *et al*. Demonstration of the transmissible agent in tissue from a pregnant woman with CJD. *New Eng J Med* 1992 327, 649.

[13] Wadsworth *et al*. Human prion protein with valine 129 prevents expression of variant CJD phenotype. *Science*. 2004 306, 1793-1796.

[14] Devereux G *et al*. Variations in neurodegenerative disease across the UK: findings from the national study of Progressive Intellectual and Neurological Deterioration (PIND). *Arch Dis Child*. 2004 89, 8-12.

Conclusions

12. In summary, there is currently no epidemiological evidence for maternal transmission of vCJD, including transmission via breast milk. However, there is a hypothetical risk. Although available evidence is limited and mostly indirect rather than direct, this risk, if any, appears to be low. As a risk cannot be excluded, a watching brief should be maintained.

Annex 9

Summary of SEAC's Discussion on the Conclusions from the RAG Meeting on the Over Thirty Month Rule Review

The FSA/SEAC Risk Assessment group (RAG) met on April 2nd 2004 to consider the impact of new data on the OTM Rule review risk assessment.

These data included the vCJD case likely to have resulted from blood transfusion and results from the retrospective tonsil/appendix study funded by Department of Health. These data had been presented to SEAC in February 2004. The FSA asked SEAC to comment on the conclusions reached by the FSA/SEAC risk assessment group.

Outcome of discussion

In terms of impact of the new data on the OTM Rule review risk assessment; both SEAC and RAG

- *agreed* that the new data do not alter the fundamental assumptions used to assess the effect of OTM rule removal (i.e. in estimating the ratio of future risk to that from past exposure).

- *agreed* that it was unlikely that the new data on the possible risk of transmission of vCJD through blood transfusion would have an important impact on the risk assessment.

- *agreed* that the finding of a case of BSE in the US and the report of atypical cases of BSE in Italy would be most unlikely to have any impact on the risk assessment.

- *acknowledged* the significant disparity between the recent prevalence data and model predictions based on the clinical case data.

- *agreed* that replacing the OTMS with testing to identify BSE infections in OTM cattle would have only a very small effect on the estimated potential overall size of the vCJD epidemic.

Opinion differed within SEAC when asked if they agreed with RAG's conclusion, based on consideration of the new data from the survey of appendix and tonsil specimens, that it was still pessimistic to assume that (historic) food borne exposure would result in a total of 5000 vCJD cases over the next 60 years.

Background

Accumulation of prion protein in lymphoreticular tissue has been consistently reported in cases of vCJD. Although it is not clear if this accumulation is limited to vCJD, so far it has not been identified in other human diseases. In a retrospective survey to screen for the presence of abnormal accumulation of prion protein in lymphoreticular tissues, 3 appendix samples out of 12,674 appendix and tonsil samples showed abnormal accumulations of prion protein. The 3 appendix samples met the criteria for positivity specified before analysis but the pattern of distribution of accumulated prion protein in

two samples differed from that previously seen in appendices from clinical vCJD cases. The atypical pattern in these samples adds to the uncertainty of the prognostic significance of these findings.

If it is assumed that all three positive samples represent infections with the vCJD agent, the prevalence of infected appendices is higher than predictions based on the clinical case data. The most recent modelling of the potential size of the vCJD epidemic, based on data on clinical cases of vCJD, suggests an upper 95% confidence interval of 540 cases.

Summary of SEAC's discussion

Both RAG & SEAC *agreed* that the disparity between the new prevalence data and model predictions based on clinical data increased the uncertainty around the estimates of cases potentially arising from historic exposure to BSE. However, opinion differed as to how this uncertainty should be handled when deriving a pessimistic estimate of the potential size of the vCJD epidemic.

Both RAG and SEAC *acknowledged* that if a pessimistic estimate were based on the new prevalence data alone, the figure of 5000 would not necessarily represent the upper limit of vCJD cases that could arise (from historic exposure) over the next 60 years. If it was assumed that all three positive appendix samples were removed from patients infected with the vCJD agent, this increased the upper limit of the epidemic to 11,000 "positive" appendices in those aged 10 - 30 years (Note, the estimate of infected individuals will be larger if a wider age range is considered and allowance made for the possibility that appendix tissue might not test "positive" throughout the incubation period of vCJD)

Both SEAC and RAG *agreed* that the key uncertainty surrounding the positive samples concerned their relationship to vCJD;

- On the one hand, it is not known if all three individuals with positive appendix samples represent individuals infected with the vCJD agent. Some or all of the positive samples might be "false positives" and may not be indicative of infection with the vCJD agent.

- On the other hand, the atypical positive appendix samples may be due to other factors, such as: infections detected at an early stage in the incubation period; infections of those of a different genotype (all clinical cases of vCJD examined to date have been methionine homozygous at codon 129 of the prion protein gene – there was insufficient material in the appendix samples to test genotype); infections through a route other than oral; or infections in chronic carriers who may not progress to clinical disease (such carriers may represent a potential source of vCJD infectivity with respect to blood transfusion, surgery, etc).

In view of these uncertainties in interpretation, RAG considered it overly cautious to base estimates of future vCJD cases solely on the new prevalence data. RAG considered it appropriate to give most weight to the clinical case data in deriving a pessimistic estimate of the size of the epidemic, given the disparity between the different data sets and the scientific uncertainty surrounding the biological significance of the

three positive samples. RAG agreed that the clinical case data should be given the most weight in deriving the estimates and concluded that it was still pessimistic to assume that historic exposure would result in 5000 vCJD cases over the next 60 years.

Divergence of scientific opinion

Some SEAC members agreed with RAG's approach. However, others considered that the new appendix data should be given most weight, despite the significant uncertainty in interpreting these data. They thought it was more appropriate to adopt a cautious approach and derive a pessimistic estimate based on the prevalence data alone and assume that all three individuals would go on to develop clinical vCJD. Thus, the divergent opinions between RAG and some SEAC members stemmed from a difference in the weight given to the different data sets rather than a fundamental disagreement *per se*.

Both SEAC & RAG *agreed* that if a pessimistic estimate were to be based on the prevalence data alone, it would lead to a small corresponding increase in the potential number of future vCJD cases arising from the OTM rule change.

Assuming a pessimistic estimate of 5000 vCJD cases from historic food-borne exposure, RAG estimated that if the OTM rule was removed, and only BSE-test negative animals were allowed into the food chain, then the additional exposure to BSE would increase the number of cases of vCJD over the next 60 years by 0.04 cases (upper limit of 2.4 cases). If the pessimistic estimate of the size of the vCJD epidemic resulting from historic BSE exposure increased from 5000, additional cases of vCJD (due to future exposure) would increase in direct proportion to the postulated increase in the size of the epidemic due to historic exposure.

SEAC

May 17th 2004

Annex 10

Updated approach to assessing the future number of vCJD cases arising from relaxation of the OTM scheme

1. The OTM rule risk assessment work carried out in 2003 suggested that allowing BSE test-negative cattle born after 1st August 1996 into the human food chain over a five year period (2004-2009) might increase the number of cases of vCJD attributable to BSE exposure by about 0.03 cases over the next 60 years (upper limit 1.9 cases). This estimate was based on an assumed "worst case" scenario that past exposure to the BSE agent in food could potentially give rise to 5000 vCJD cases (over the next 60 years). The number of 5000 was an illustrative figure that represented a pessimistic upper limit, taking into account predictions of epidemic size based on annual numbers of vCJD deaths to date. It was not derived from a statistically-based confidence interval.

2. SEAC considered findings reported recently from a retrospective survey of prion protein accumulation in appendix and tonsil tissue to assess if this "worst-case" scenario continues to be appropriate. The committee discussed whether a total epidemic size of 5000 remained pessimistic in the context of new data on the prevalence of infection based on a retrospective study of appendix/tonsil tissue. Opinion was divided among SEAC members. Some considered that the figure of 5000 remained an appropriate pessimistic upper limit, others favoured basing the upper limit on the results of the, then unpublished, appendix/tonsil survey.

The updated analysis

3. The FSA commissioned a group at Imperial College to update the OTM risk assessment, taking account of the new data and improving the statistical rigour of the analysis.

4. The 2003 analysis considered combined "worst case" scenarios with respect to (i) the amount of infected material that might enter the human food chain (following a change in the OTM rule), as a proportion of all such material entering the food chain since the BSE epidemic started, and (ii) the possible total size of the vCJD epidemic. The new analysis took simultaneous account of uncertainty in both these scenarios. These uncertainties were considered jointly in a statistical analysis to provide estimates (and associated confidence intervals) of vCJD cases arising from exposure in the 2004-2009 periods that would be attributable to a change in the OTM rule. Because of the difference of view within SEAC with respect to the relative weights to be given to different methods of projecting the total size of the vCJD epidemic, separate analyses were conducted basing this projection (i) on the retrospective appendix and tonsil survey data alone, or (ii) on the annual numbers of vCJD deaths observed since 1996, alone.

5. The new analysis extends the work of the 2003 analysis and considers in an integrated and probabilistic manner uncertainties in the BSE modelling and in the vCJD predictions.

Update to BSE analysis

6. Two conservative assumptions were made in calculating the proportion of infectious material that would enter the food chain between 2004 and 2009 consequent on a change to the OTM rule. These assumptions were also used in the 2003 OTM risk assessment.

i. The assumption of a constant BSE infection rate for future cattle cohorts.

It is clear that the August 1996 feed ban did not completely eliminate BSE infection as some cattle born after that date have been diagnosed with BSE. The latest date for which modelling of the BSE epidemic can provide an estimate of the level of infection is 1999. Two plausible assumptions are (i) that the infection level in the 1999 birth cohort will not diminish in later cohorts and will continue at the same level to 2009, or (ii) that the infection level declines in cohorts born after January 2001 (the date of the EU-wide feed ban). The updated analysis, like the 2003 analysis, used the more conservative of these two assumptions and assumed the infection risk will not diminish.

ii. The assumption of low BSE test sensitivity.

Studies coordinated by the EU have shown that the current BSE tests have very high sensitivity among cattle showing clinical signs of BSE infection. However, due to the variation in the incubation period for BSE, it is not possible to determine how sensitive current BSE tests are prior to clinical onset. The updated analysis was based on the conservative assumption that the test will only pick up infected animals in approximately the last 3 months prior to clinical disease (as was also assumed in the 2003 analysis).

7. A number of assumptions regarding **differential mortality** were used in the modelling. These assumptions allow for the possibility that BSE-infected animals, but without recognised signs of BSE, will die or be slaughtered at an earlier age than BSE-uninfected animals. This assumption has been included in previous modelling and found to improve the fit of the model, particularly with respect to explaining the relatively high level of BSE test positivity among OTMS casualty animals. The new analysis examined several periods for differential mortality ranging from 3 months before onset to one year before onset.

8. Using the assumptions given above, estimates were derived of the number of infected cattle, at different stages of their incubation periods, that would be consumed over a five-year period (2004-2009) associated with changing the OTM rule. By integrating these data with estimates of residual infectivity in different tissues at different stages of the incubation period, estimates were obtained of the likely extent of human exposure (measured in bovine infectious units). These estimates were compared with estimated historic exposure so that future exposure over a five year period, from 2004 – 2009, could be expressed as a percentage of past exposure (before 2004). Options were considered in which only healthy animals or healthy and casualty animals were allowed to enter the food chain.

Predicting the total size of the vCJD epidemic

9. The recently published data from the retrospective appendix and tonsil survey suggest that the prevalence of infections may be higher than predictions based on the clinical case data alone. In view of the variance in the views of SEAC members about the interpretation of these data, the new analysis based predictions of future vCJD infections (arising from OTM rule change) on the most conservative scenario. This scenario was based on estimates of prevalence of infection with the vCJD agent derived from the appendix/tonsil survey data and the assumption that all three positive samples, reported in the study, represent infections with the vCJD agent that would progress to clinical disease.

10. The tonsil/appendix survey related predominantly to individuals aged 10-30 years old and it is necessary to make assumptions to extrapolate findings to other age groups.
    It could be assumed that the occurrence of vCJD cases in different age groups reflects the relative infection rates in different age groups. Alternatively it might be assumed that all individuals had similar susceptibility/exposure irrespective of their age and that the findings in the 10-30 year old group could be applied directly to other age groups. Both of these possibilities were included in the modelling.

11. A further assumption was made that despite the finding, to date, that all cases of vCJD have been homogenous for methionine at codon 129 of the *PRPN* gene; all genotypes were equally susceptible to vCJD.

12. The new analysis also considered variation in the appendix/tonsil test sensitivity, that is, the proportion of all infected individuals who would test positive. The test may not detect all infected individuals and it would be appropriate to assume a sensitivity of less than 100%. However, there are few data to guide the choice of a sensitivity level.

Outcome of SEAC discussion

13. Four additional experts with expertise in risk modelling and epidemiology attended the meeting to advise SEAC and provide a peer review of the modelling methodology. The additional experts are listed in Annex 1

14. SEAC and attending experts welcomed the new analysis by the group from Imperial College and agreed that the approach was more appropriate than that used previously. They endorsed the methodology of integrating the BSE modelling and the vCJD data to estimate the number of vCJD infections arising from changes to the OTM rule and associated uncertainties. They agreed that the analysis provided a more defensible approach than the 2003 analysis as it took simultaneous account of uncertainties at different stages of the modelling. They agreed that estimation of confidence limits improved the statistical rigour of the risk assessment.

15. SEAC acknowledged that the estimates of the number of vCJD infections attributable to the OTM change are dependent on the various assumptions made in the analysis. However, even with the conservative assumptions recommended for the updated analysis, a change to the OTM rule would contribute a very small number of future infections relative to the number of infections attributable to past exposure.

16. SEAC were asked to advise on which assumptions would be most appropriate to account for the range of scientific uncertainties. It was agreed that the following assumptions were appropriate in generating estimates to be presented to the FSA board to consider the risk management options for changing the OTM rule.

BSE modelling

17. In terms of the BSE model, SEAC and attending experts agreed that two of the key assumptions used in the analysis were still appropriately conservative (constant infection risk after 1999 and low sensitivity of BSE tests beyond 3 months from BSE onset).

18. SEAC agreed that it was conservative, but prudent, to use a worst-case scenario to account for the possibility that differential mortality in BSE infected animals could occur within the last 12 months of the incubation period, rather than a shorter period. SEAC recognised that this was likely to be pessimistic but in view of the paucity of the data on this issue, SEAC agreed it was an appropriate precautionary stance.

vCJD epidemic size

19. SEAC agreed that the new developments have increased the scientific uncertainty around predictions of the evolution of the vCJD epidemic. They agreed that a pessimistic approach would be to base predictions of the vCJD epidemic on the prevalence data alone (from the appendix/tonsil survey) rather than on the clinical case data.

20. SEAC agreed that in view of the lack of data and the significant uncertainty it was appropriate to assume that the testing used in the appendix/tonsil survey would identify only 50% of individuals infected with the vCJD agent. SEAC recommended that the analysis should be revised for the FSA board to assume this level of sensitivity.

21. SEAC agreed that it would be overly cautious to dismiss the clinical case data in informing the assumption on age dependent susceptibility/exposure. Therefore they agreed that in estimating prevalence levels of infection it was appropriate that the estimates should be adjusted, taking into account the age distribution of cases of vCJD. Furthermore, all genotypes should be assumed to have similar susceptibility.

Recommendations on presentation to the FSA Board

22. SEAC noted that estimates were presented as two options, either that healthy animals only or a combination of healthy and casualty animals were allowed into the food chain. SEAC noted that although the number of casualty animals entering the food chain was relatively small, casualty animals contributed disproportionately to the level of risk if the OTM rule were changed. While this is unsurprising as the majority of BSE positives have been found in casualty animals, SEAC agreed that the inclusion of casualty animals increases the risks associated with changing the OTM rule and suggested that the FSA Board note this when considering the risk management options.

23. SEAC noted that the risk assessment was limited by the paucity of data and significant scientific uncertainties remained. Despite the use of "pessimistic scenarios" throughout the analysis, the lack of data meant that some components of the risk assessment were based on expert judgement rather than being fully informed by all the required data. It is important that Government is made aware of this.

24. SEAC recommended that when the risk assessment data are presented to the FSA board, it was important that they should also be provided with the corresponding estimate of the total size of the epidemic so that the numbers of additional cases attributed to changing the OTM rule can be seen as a proportion of all cases of vCJD.

Annex 11

Summary of Discussion on BSE & Sheep: the FSA Contingency Policy

The committee was provided with background information on the analytical techniques used to detect and discriminate BSE and scrapie in sheep samples, and the preliminary results from an on-going ring-trial comparing the analytical methods used by different research groups.

SEAC was also presented with the findings from two studies modelling the:

- maximum number of sheep that could potentially be infected with BSE in the GB sheep flock based on testing results from retrospective and prospective surveillance of TSEs in sheep;

- potential BSE infectivity in sheep together with strategies to reduce the risk of BSE infectivity entering the food chain based on a) the relative susceptibilities of sheep genotypes to BSE infection, b) removal of specified risk materials or c) TSE testing.

TSE test methods

SEAC noted that the analytical methods used to detect TSEs in sheep, and distinguish BSE from scrapie, were becoming more robust. A combination of tests now provides a reasonably rigorous, although not completely unambiguous, approach to distinguishing conventional scrapie from conventional BSE in sheep. The results from the on-going ring-trial will be important to assess more fully the robustness of the methods. It was considered important to analyse final data from the conformation-dependent immunoassay (CDI) method in the ring-trial because, unlike all the other methods used, it does not rely on differential enzyme (Proteinase K) digestion of the prion protein (PrP). Thus, it could be an important and possibly powerful additional discriminatory test.

SEAC considered that, using the currently available tests, the vast majority of the TSE's detected in sheep in prospective and retrospective surveys were likely to be scrapie and not BSE. Furthermore, no unambiguous case of BSE in sheep has yet been detected. Nevertheless, because of limitations in methodology and the number of samples tested this conclusion cannot be considered certain.

SEAC noted that two surveillance samples had given atypical test results that were inconsistent with the criteria used to define either BSE in sheep or scrapie infection. It was considered possible that these two atypical TSE test results could indicate the presence of a variant form of scrapie, a variant form of BSE, another as yet uncharacterised TSE, or reflect a modifying effect of a particular sheep genotype. It was noted that tests of orally transmitted and passaged BSE in all sheep genotypes had not yet been conducted. The committee agreed it was very important to conduct more research to try to establish the nature of these samples and particular urgency should be given to in vivo infectivity studies.

Possible prevalence of BSE in sheep

SEAC generally accepted the approach used to model the possible prevalence of BSE in sheep. However, it was noted that the model depended on the ability of the tests used to effectively detect and discriminate between scrapie and BSE and current tests were not yet 100% reliable (see above).

Perhaps more significantly, SEAC considered that, because many of the samples included in the surveillance had come from farms with a large number of scrapie cases, which may be more likely to report scrapie cases, the data may have been influenced by a selective ascertainment bias. It was agreed that basing the calculation of the prevalence of BSE in sheep on TSE affected flocks, rather TSE cases, was preferable. Nevertheless, even if only flocks are considered, the effect of non-random sampling may have led to an underestimation of the number of potential BSE cases. It was suggested that that if the modelling was restricted to the results obtained from active surveillance the bias could be minimised, although such an analysis would significantly reduce the data that could be included in the model. Additionally, it was suggested that data from a 2002 scrapie postal survey, relating to the distribution of cases on scrapie affected farms, could be compared with the passive surveillance data in order to assess the possible effect of the sample bias.

Impact of risk reduction strategies

SEAC generally accepted the modelling approach used and acknowledged that it was extremely difficult to estimate the potential BSE infectivity entering the food chain from tissues of infected sheep. The committee noted that the model of BSE infectivity in sheep was based on a large number of assumptions. For example, the model assumed that the pathogenesis of BSE and scrapie in sheep may be similar, yet this is still largely unknown. In addition, although ARR homozygous sheep appear to be the most resistant PrP genotype, sheep of this genotype could not now be considered to be completely resistant to TSE infection. SEAC noted that, in contrast to the assumptions made in the modelling, sheep breeds were heterogeneous and methods of husbandry differed considerably between farms. Also, it may not be appropriate to generalise about the prevalence and distribution of PrP genotypes in sheep because PrP genotype can extremely variable between different sheep breeds.

It was noted that estimates used for the quantity of sheep tissues entering the food chain differed from values used by other research groups. In addition, the effective removal of lymph nodes was considered unrealistic.

Bearing in mind these assumptions and caveats, SEAC noted that:

- the model of BSE infectivity in sheep tissues suggested that a single BSE infected sheep entering the food chain could present a significantly greater risk to public health compared with the current risk associated from a single infected cow;

- although there was no evidence of a large self-sustaining epidemic of BSE in sheep, the model suggests that the presence of small epidemics in a few flocks cannot yet be ruled out;

- the models suggest that strategies based on control of specified risk material or TSE testing are currently unlikely to be very effective in minimising risk of human infection. The committee considered that should the sensitivity of TSE tests be improved they may be effective in the future.

- the model suggests that strategies based on the PrP genotype of sheep would be the most effective in reducing risk of human infection. However, the committee stressed that the magnitude of the relative reductions in risk between the various strategies modelled could not be regarded as absolute.

Secretariat 11 October 2004

Annex 12

Position Statement on Chronic Wasting Disease in UK Deer

Introduction

1. The Food Standards Agency asked SEAC to consider the possible public and animal health implications of chronic wasting disease (CWD), in particular the level of risk posed to consumers of meat from infected animals. The committee also considered the possibility that BSE may be present in UK deer.

Background

2. CWD has emerged as an endemic transmissible spongiform encephalopathy (TSE) in certain captive and free-ranging species of cervid (deer) in some areas of North America. The disease is characterised by weight loss and behavioural changes in infected animals, usually over a period of weeks or months leading to death. CWD has not been found in the UK or elsewhere in Europe. No definitive or suspected cases of transmission of CWD to humans have been reported.

3. SEAC considered a review of the published, and some unpublished, research on CWD, together with surveillance data on TSEs in European cervids and information on UK cervid populations[15].

Origins

4. The origins of CWD are unknown. On the basis of epidemiological data, it is highly improbable that CWD originated from the recycling of mammalian protein in processed feed. It has been suggested that CWD may have arisen from transmission and adaptation of scrapie from sheep to cervids, as a result of a spontaneous change of endogenous prion protein (PrP) to an abnormal disease-associated form, or from an unknown source.

5. Data supporting any of these possible origins of CWD are either absent or equivocal. Although CWD could have originated from scrapie, the differing properties of the two prion diseases in strain typing bioassays, whilst limited, do not support this hypothesis. Evidence for multiple strains of CWD is equivocal. It seems most likely that CWD arose from a spontaneous change of endogenous PrP resulting in a disease-associated and laterally-transmissible form of PrP, although direct data to support this hypothesis are lacking.

Host range

6. The known natural hosts for CWD are mule deer (*Odocoileus hemionus hemionus*), black-tailed deer (*Odocoileus hemionus columbianus*), white-tailed deer (*Odocoileus virginianus*) and Rocky Mountain elk (*Cervus elaphus nelsoni*). The prevalence and geographical distribution of CWD in these species appears to be

[15] The information considered by the committee is available at: http://www.seac.gov.uk/agenda/agen301104.htm

increasing in North America in a manner which is unlikely to be due simply to increased surveillance.

7. There are no direct data relating to the transmissibility of CWD to UK cervid species. However, comparison of a limited number of PrP codons indicates some homology in the endogenous PrP gene of European and North American cervid species. Thus, the possibility that UK cervids may be susceptible to CWD cannot be excluded, in particular red deer (*Cervus elaphus elaphus*) which are closely related to elk.

8. There is no evidence to suggest that CWD is present in UK cervids. However, because surveillance in the UK is very limited, a low level prevalence of CWD cannot be ruled out. The committee endorsed the opinion of the European Food Safety Authority on CWD surveillance in the European Union (2004)[16].

9. Transmission studies using parenteral routes of administration to cattle, sheep and a single goat, together with data from *in vitro* PrP conversion experiments, suggest that a significant barrier to CWD transmission to these species may exist. No transmission has been evident so far in an on-going oral transmission study in cattle after six years. Furthermore, no signs of infection have been observed from monitoring of cattle co-habiting areas with infected cervids, or in cattle, sheep or goats in close contact with infected cervids in research facilities. Thus, although the data are limited, there is currently no evidence to suggest that CWD can be transmitted naturally to cows, sheep or goats, and it is likely that there is a strong species barrier to such transmission.

Routes of transmission

10. Epidemiological data indicate that lateral transmission between infected and susceptible cervids occurring naturally is sufficiently effective to maintain epidemics in both captive and free-living populations. There is good evidence from studies of cervids inhabiting paddocks previously inhabited by infected animals or contaminated with infected carcases, that CWD can be transmitted laterally between animals via the environment. The precise mechanism of transmission is unclear. It is possible that the infectious agent is shed in the saliva, faeces or urine or as a result of decomposition of infected carcases and transferred to other cervids grazing the contaminated areas. It is also possible that some maternal transmission occurs.

11. There have also been suggestions that the lateral transmission of CWD may be influenced by environmental factors.

Pathogenesis

12. Information on the pathogenesis of CWD is limited. The data show that, following oral challenge, PrP^{CWD} is first detected in the oral and gut-associated lymphoid tissues before spreading more widely within the lymphoid system and then to the brain. Involvement of the retropharyngeal lymph nodes or tonsils in the

[16] http://www.efsa.eu.int/science/biohaz/biohaz_opinions/501_en.html

pathogenesis may not occur in some elk. At the microscopic level, the nature and distribution of the tissue lesions are similar to those found for scrapie. The available data suggest the pathogenesis of CWD is similar to scrapie.

BSE in UK deer

13. Both captive and free-ranging cervids in the UK may have been exposed to contaminated feed prior to the reinforced mammalian meat and bone meal ban instituted in 1996. A study to look at the potential susceptibility of red deer to BSE has shown no signs of transmission of the disease by the oral route, but it is at a very preliminary stage. Although a theoretical possibility exists, there is no evidence from the very limited surveillance data to suggest that BSE is present in the UK cervid population.

Human health implications

14. Epidemiological data on possible CWD infection of humans are very limited. The possibility that clinical symptoms of CWD in humans differ from those of Creutzfeldt-Jakob Disease (CJD) cannot be excluded. There is no significant difference between the prevalence of CJD in CWD endemic areas and other areas of the world. However, because CJD surveillance in the USA is relatively recent, not all CJD cases may have been identified. Additionally, detection of a small increase in prevalence of such a rare disease is very difficult. Investigation of six cases of prion disease in young people (< 30 years of age) in the USA found no definite causal link with consumption of venison from known CWD endemic areas. The disease characteristics in these cases were indistinguishable from sporadic CJD or Gerstmann-Sträussler-Scheinker syndrome. Likewise, in a study of three hunters (> 54 years of age) diagnosed with sporadic CJD, no link with consumption of venison from CWD endemic areas was found. No causal link was found in an investigation of three men with neurological illnesses who were known to partake in "wild game feasts". Only one of these subjects was found to have a prion disease and this was also indistinguishable from sporadic CJD.

15. Preliminary results from transmission experiments in transgenic mice expressing human PrP suggest the presence of a significant species barrier to transmission of CWD to humans. However, these findings must be interpreted with caution as they may not accurately predict the human situation. Data from *in vitro* experiments on conversion of human PrP by disease-associated forms of PrP, including PrP^{CWD}, are equivocal.

16. The committee concluded there is no evidence of transmission of CWD to humans from consumption of venison, and that there may be significant barriers to transmission. Nevertheless, as the data are extremely limited a risk cannot be ruled out should CWD enter UK herds.

Conclusions

17. There is no evidence that CWD (or BSE) is present in the UK cervid population. However, because only limited surveillance is conducted in the cervid population, a

low level prevalence of CWD cannot be ruled out. It is recommended that further surveillance of TSEs in UK cervids is conducted.

18. There is no evidence of transmission of CWD to humans from consumption of meat from infected cervids. Although epidemiological and experimental data on potential transmission of CWD are extremely limited, they suggest that there may be a significant species barrier. It would be helpful if further studies were available assessing the potential species barrier for transmission to humans.

19. Although limited, there is no evidence CWD can be transmitted to cattle, sheep or goats by natural means.

20. In summary, it appears that CWD currently poses relatively little risk to human health, or to the health of cattle, sheep or goats in the UK. Nevertheless, as a risk cannot be excluded a watching brief should be maintained.

Annex 13

SEAC Sheep Subgroup Consideration of Options for the National Scrapie Plan

Options for the NSP

Option A- EU minimum

The EU minimum rules require the genotype testing of all rams intended for breeding within flocks of 'high genetic merit' (Defra are proposing to apply the definition of 'high genetic merit' to all pure-bred flocks which sell homebred rams for further breeding) and the subsequent slaughter of those found to be carrying the VRQ allele (compensation will be paid for animals slaughtered). It does not require the genotype testing of rams sold for breeding elsewhere. Consequently, the sale of untested (and hence possibly VRQ) rams for further breeding is not prohibited. However, any untested rams purchased for use within another flock of 'high genetic merit' would need to be genotyped before being used for breeding and those carrying the VRQ allele removed in line with the requirements of the EU legislation.

Option B- EU minimum plus additional genotyping of rams/shearlings/ram lambs intended for sale and further breeding elsewhere

In addition to the EU minimum requirements as described above at Option A, this option would also provide for the genotype testing in all flocks of 'high genetic merit' of rams\shearlings\ram lambs intended for sale and further breeding irrespective of whether they are to be used in other flocks of 'high genetic merit' or elsewhere further down the breeding pyramid e.g. in a commercial fat\slaughter lamb producing flock.

Option C- EU Minimum plus additional ram testing as Option B and voluntary ewe testing during the period 2005-2010 conditional on the removal of ARQ/ARQ breeding rams in participating flocks from 2010

As Option B above, with an additional voluntary ewe genotyping scheme\service targeting female replacements conditional on the removal of ARQ/ARQ breeding rams from participating flocks from 2010. The Option is currently based on testing 200,000 female replacements across all sheep sectors per year. This is an indicative figure based on possible field and laboratory testing resource considerations (and may require fine tuning).

Option D- Compulsory NSP Ram Genotyping Scheme (RGS)

The current voluntary NSP's RGS provides for the genotyping of all existing stock rams and for the removal of those carrying the VRQ allele. It also applies sale and on farm use restrictions for Type 3 (ARQ\AHQ\ARH) rams (end 2005 and 2008 respectively for terminal sire breeds and end 2007 and 2009 respectively for hill breeds). Additionally, it also provides for annual progeny testing of males (and females where there are fewer than 40 male animals available for testing i.e. each testing visit will comprise 40 animals in total) intended for further breeding. Under Option D, these arrangements would be made compulsory for all flocks of 'high genetic merit'.

Option E

Strategy B (implementation of the minimum requirements set down in EU legislation (EU 2003) with the addition of sale restrictions on VRQ-bearing rams for all flocks of high genetic merit from 2005) and voluntary implementation of the current NSP purebred flock scheme.

Option F

Strategy E with the addition of ewe genotyping (and removal of VRQ-bearing ewes) in those flocks participating in the voluntary NSP scheme.

SEAC Sheep Subgroup Statement on Options for the NSP

Defra is consulting stakeholders on four strategic options for the future operation of the National Scrapie Plan (NSP). The SEAC sheep subgroup's views were sought as part of this consultation.

The subgroup concluded that the strategy of the NSP underlying breeding for scrapie resistance remains appropriate. However, the basis for the strategy should be kept under review in the light of emerging scientific findings with respect to the possible detection of scrapie infections in animals of genotypes currently thought to be most resistant to infection.

The subgroup was of the view that those strategies that reduced the prevalence of infection in the national flock most rapidly were the most desirable. On this basis Option A was considered inadequate. The subgroup considered that although Options A and B addressed scrapie in VRQ sheep these would not reduce scrapie in ARQ sheep, which may be more susceptible than assumed in the modelling, or the hypothetical possibility of BSE in sheep, which appears to preferentially target the ARQ allele. The subgroup considered a solution close to Option D was the most scientifically desirable given the importance of reducing the prevalence of scrapie and the potential risk of BSE.

The subgroup recognised there may be potential practical difficulties and in some cases genetic constraints for the sheep industry as well as cost issues associated with option D and therefore recommended that an additional option, Option E (mandatory Option B combined with voluntary Option D) be considered. This option, together with a further option, Option F (Option E combined with voluntary ewe genotyping and removal of VRQ ewes) were modelled. The subgroup considered the outcome of the additional modelling work and agreed that Option D remains the most scientifically desirable. Option F offered no significant advantage over Option E. Members agreed that Option E, given high voluntary take up, was also a scientifically valid strategic option for the NSP.

SEAC sheep subgroup (13 October 2004)