SEAC

Spongiform Encephalopathy
Advisory Committee

ANNUAL REPORT 2002

(April –December)

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Main Topics Considered by SEAC

Foreword

I am pleased to present this, the sixth Annual Report of the Spongiform Encephalopathy Advisory Committee (SEAC) covering the period 1 April 2002 to 31 December 2002. Future SEAC annual reports will reflect the work of the committee on a calendar year basis.

The BSE epidemic in cattle has continued to decline in line with expectation. Statistical evidence suggests that the vCJD epidemic may no longer be increasing at the rate seen previously. This is an encouraging sign but cannot, as yet, be regarded as definitive evidence that the epidemic has peaked and is in decline. A large proportion of the committee's time has been occupied with advising on the consequences of infections in humans, particularly vCJD infectivity in blood and the transmission of prion diseases by blood transfusion. Other issues considered by the committee included the epidemiological predictions undertaken as part of the Food Standards Agency (FSA) review of the Over Thirty Month Rule, intraspecies recycling and a study on BSE and milk.

The period covered by this report saw significant change in the way the committee operated. The work of the committee continues to invoke much public interest and in 2002 SEAC moved to holding regular meetings in public. This allows the public to observe the committee at first hand and provides an excellent insight as to how Government procures independent scientific advice. The move to public meetings coincided with the formation of a dedicated cross-departmental secretariat, with a single SEAC secretary to support the work of the committee. I would therefore like to thank the three departmental secretaries and support staff, together with the current secretary and secretariat staff that provided me with valuable support during this transitional period.

As always, I am very grateful to my fellow committee members who contribute their valuable time to discuss the important issues brought before the committee. I would particularly like to acknowledge the important contributions made over a number of years by Professor John Collinge, who left the committee during this period. Professor Collinge's knowledge of neuropathology and his work and experience at the Medical Research Council Prion Unit has been of great value to the deliberations of SEAC.

The committee continues to be reliant upon access to early research findings and technical briefings on particular issues and I would like to thank those who throughout the year have helped the committee by providing this valuable information.

Professor Peter Smith
Chairman

About the Committee

1. SEAC is an independent expert advisory committee. Its terms of reference are to provide scientifically-based advice to the Department for Environment, Food and Rural Affairs (Defra), the Department of Health (DH), the Food Standards Agency (FSA) and the Devolved Administrations on matters relating to spongiform encephalopathies, taking account of the remits of other bodies with related responsibilities.

2. SEAC evolved as a reconstitution of the Tyrrell Committee, which in turn had emerged from the Southwood Working Party. The Tyrrell Committee and its predecessor the Southwood Working Party were the bodies that originally advised the government on BSE related issues.

3. SEAC held its inaugural meeting on 1 May 1990 and since then has advised the Government on public health matters, food safety and animal health implications relating to transmissible spongiform encephalopathies (TSEs).

4. SEAC is a Public Body whose members are appointed to the committee in accordance with the code for public appointments issued by the Commissioner for Public Appointments. It is based on the Nolan Principles, which aim to ensure fairness and transparency in appointments.

5. The committee meets five or six times a year to formulate advice on scientific aspects of TSEs. Government consider SEAC's advice when formulating public and animal health policies.

6. Committee discussions can include the following:

   - Specific requests from Ministers and officials for advice.
   - Implications of new research.
   - Requests from a member of the committee.

The Committee's Commitment to Openness

7. SEAC has continued to increase the openness and transparency of its meetings and 2002 saw a significant step forward in this respect. Following the success of SEAC's open meeting in September 2001, it was agreed that future meetings should be held in open session. This took effect from September 2002, and the public are now invited to observe the committee at work by attending the open meetings.

8. The committee publishes much of its work on the SEAC web site (www.seac.gov.uk), including agendas, meeting papers, minutes, annual

reports and statements. Contact details for the secretariat are also available on the SEAC web site so that queries can be submitted or to register for attendance at an open meeting.

9. However, there are occasions where certain issues cannot be discussed in open session, such as unpublished or pre-publication data. These topics are considered in a reserved business session. Once the information has been published, the committee is free to release the details of its discussion into the public domain. The SEAC Code of Practice, which is available on the SEAC website, provides a more detailed explanation of the type of items that may be considered in reserved business.

Meet the Members

10. Members of SEAC are usually appointed for a period of three years. The Commissioner for Public Appointments Code considers that renewal for a further 3 years, but not longer, is permissible.

11. During the period covered by this report, SEAC membership consisted of experts from wide-ranging scientific backgrounds including epidemiology, neurology, neuropathology, veterinary science, genetics and public health practice. One committee member (Professor Harriet Kimbell) represented the public interest.

Professor Peter Smith (SEAC Chair)
Head of 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

Professor Roy Anderson
Head of the Department of Infectious Disease Epidemiology, Imperial College School of Medicine, University of London

Professor Christopher Bostock
Director of the Biotechnology & Biological Sciences Research Council's Institute for Animal Health

Professor Graham Bulfield
Vice-Principal and Head of the new College of Science and Engineering at the University of Edinburgh

Professor Robin Carrell
Professor of Haematology at the University of Cambridge

Professor John Collinge
Director and the Head of Department, MRC Prion Unit and Department of Neurodegenerative Disease, Institute of Neurology

Dr Deirdre Cunningham
Public Health and Medical Director of the Southeast London Strategic Health Authority

Professor James Ironside (Deputy Chair)
Neuropathologist at the National CJD Surveillance Unit, Edinburgh

Mr Peter Jinman
Private Veterinary Surgeon and President of the British Veterinary Association

Professor Harriet Kimbell MBE
Associate Professor at the Guildford College of Law and a member of the Council of the Consumers' Association

Professor Colin Masters
Professor and Head of the Department of Pathology, University of Melbourne, Australia

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

Dr Jiri Safar
Adjunct Associate Professor in the Department of Neurology at the University of California, San Francisco

Code of Practice for Members

12. The SEAC Code of Practice (COP) gives specific guidance on publication of work by SEAC Members, conflicts of interest and confidentiality. The COP contains guidance on the disclosure of Committee business after SEAC meetings and information on an indemnity offered by Ministers to Members of SEAC and related Committees in connection with the performance of Committee duties. A copy of the indemnity offered to SEAC Members can be found at Annex II. The SEAC COP is guided by the seven principles of public life identified by the Nolan Committee in their report on Standards in Public Life. Copies may be obtained from the SEAC Secretariat or can be found on

the SEAC Website: http://www.seac.gov.uk/CoP_index.htm. The COP was last revised in 1999.

Register of Members Interests

13. 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 III.

Conflicts of Interest

14. In addition to the register of members' interests, members are asked to declare any conflicts of interest with respect to individual agenda items.

Secretariat

15. The Secretariat co-ordinates the work of the committee and arranges the financing of its activities. The contact address for the Secretariat (including website addresses) can be found at Annex X.

Subgroups

16. The Chairman of SEAC can authorise *ad hoc* subgroups to consider specific scientific areas in greater depth. Subgroups have specific terms of reference and are required to report to the main committee. Members of SEAC can also serve on these subgroups. There is considerable flexibility about how subgroups are set up, depending on the issues under consideration.

17. Expanded use of subgroups, as recommended in the 1997 SEAC Review, has allowed the committee to delegate the initial consideration of highly specialised issues. These require a substantial input from experts in addition to those on the main committee.

18. The SEAC Epidemiology subgroup was set up in September 1997 to assess the epidemiology of vCJD and develop advice on trends in the disease. The group meets twice a year, is chaired by Professor Peter Smith and reports jointly to the four UK Chief Medical Officers and SEAC. Membership of the Epidemiology subgroup is given at Annex IV.

19. Other subgroups, such as the SEAC Sheep subgroup convene on an *ad hoc* basis as required. The Sheep subgroup met in December 2002 to discuss issues relating to the National Scrapie Plan (NSP). Membership of the SEAC Sheep subgroup is given at Annex V.

Working groups

20. In addition to subgroups, SEAC maintains a joint working group with the Advisory Committee on Dangerous Pathogens (ACDP), chaired by Professor Don Jeffries (ACDP Member). Membership of the joint working party is given at Annex VI. The terms of reference for this Group are:

    - Consider the risks from exposure to the agents of transmissible spongiform encephalopathies that may arise as a result of work activities.

    - Develop guidance to minimise such risks.

    - Provide advice as requested by the parent Committees (ACDP and SEAC).

Main Topics Considered by SEAC

Summary

21. SEAC met four times and the Sheep and Epidemiology subgroups met once and twice respectively between 1 April 2002 and 31 December 2002. During this period SEAC and its subgroups reviewed current research within the field of transmissible spongiform encephalopathies, monitored epidemiological data on vCJD and BSE, discussed issues relating to the National Scrapie Plan (NSP) and dealt with requests for advice from government departments. New research was considered either in the form of published papers, confidential pre-publication drafts or research updates.

A. CJD and Public Health

Incidence of vCJD

22. The committee were updated at each meeting on the number of vCJD cases in the United Kingdom and worldwide. By November 2002, the total number of definite and probable vCJD cases in the UK was 128, of which 11 cases were still alive. By the end of 2002, six cases of vCJD had also been reported in France and one case each in the Republic of Ireland, Italy, the United States of America and Canada. The cases reported in Ireland, Canada and USA had a history of visits to, or residence in, the UK during the late 1980s. The cases from France and Italy did not have a history of residence in the UK. The committee noted the relatively high incidence of vCJD cases in France compared with the relatively low level of reported BSE cases in France and agreed that this could be due to the considerable number of carcasses from older UK cattle that were exported to France before the export ban. It was noted that all of the vCJD cases tested (n=105) were methionine homozygous at codon 129 of the prion protein.

23. Throughout 2002, the total number of referrals of suspected cases of vCJD to the National CJD Surveillance Unit (NCJDSU) had declined.

Predictions of future vCJD cases

24. In November 2002, analysis of the quarterly data from UK cases (produced by the Public Health Laboratory Service) for onset of, and death from vCJD were presented to the committee. There was statistical evidence to suggest that the vCJD epidemic was no longer increasing at the rate seen previously as analysis of these data showed a significant departure from an exponential increase. Both the Epidemiology Subgroup and SEAC agreed these

preliminary results were encouraging but it was premature to conclude that the epidemic had reached a peak. More data would be required before it was possible to forecast longer-term trends of the vCJD disease with any confidence.

Vaccination history of vCJD cases

25. In April 2002, the committee reviewed an investigation by the NCJDSU into the vaccination histories of a total of 69 vCJD cases. The investigation showed the average number of vaccine doses received by each vCJD case was 7 (range 1-23). Two pairs of vCJD cases who received polio vaccines from the same batch in 1994 were identified. Another two vCJD cases had received diphtheria/tetanus vaccine from the same batch in 1995. Preliminary analysis found no link between the vaccine and development of vCJD. The committee expressed their concern at the low level of recording of batch numbers of vaccines by GPs and recommended that accurate record keeping was required. The committee agreed that the probability that pairs of cases would share the same vaccine batch number increased as more vCJD cases were reported.

Testing of MRC 5 cells for abnormal prion protein and infectivity

26. In April 2002, the committee were updated on preliminary results from a study recommended by SEAC in November 2001. The study was designed to investigate if abnormal prion protein or infectivity was present in the MRC5 cell line, which was used in the production of the oral polio vaccine. The bovine Foetal Calf Serum (FCS) used in culturing the cell line was thought to be a potential source of risk. Records held at the National Institute of Biological Standards and Control (NIBSC) showed that UK bovine FCS had not been used to produce oral polio vaccine from MRC5 cells for over 20 years. Prior to 1985, FCS had been sourced from New Zealand or the USA. The protein and infectivity assays (using vCJD/BSE brain homogenate as positive controls) to detect abnormal prion protein at various passage levels were underway at NIBSC. The committee requested that the results of these tests be made available to them when the studies were completed.

Prion protein in mouse skeletal muscle

27. In April 2002, the committee considered research by Bosque *et al* (2002)[1] on the expression of abnormal prion protein in mouse skeletal muscle. Western blotting had shown wild-type mice expressed normal prion protein in skeletal muscle at a much lower level than that present in the brain. Wild-type mice

[1]Bosque PJ, Ryou C, Telling G, Peretz D, Legname G, DeArmond SJ, Prusiner SB. Prions in skeletal muscle. *Proc Natl Acad Sci U S A*. 2002;**99**:3812-7.

were inoculated intracerebrally (i.c.) with brain homogenate from scrapie infected mouse or hamster. Those that reached clinical disease were analysed for expression of scrapie prion (PrP^{Sc}). Based on an incubation time assay in transgenic mice over-expressing the mouse prion, infectivity levels in muscles were around 1/10,000 of that present in the brain. Confirmation of these findings by Western blotting showed that abnormal prion protein was confined to hind limb muscles at titres around 1/1000 of that in brain.

28. The committee agreed that this research could not directly be applied to BSE in cattle, scrapie in sheep or vCJD in humans. The committee reiterated its previous advice that decontamination of surgical instruments is key in minimising any potential for person-to-person spread of vCJD as a result of a health-case procedure. It was concluded that the findings did not alter the assessment of the risk to humans from consumption of beef.

Risk assessment of exposure to vCJD infectivity in blood and blood products

29. In June 2002, the committee were asked to advise on a draft risk assessment prepared by DNV Consulting on the potential risk of exposure to vCJD via medical treatment with blood components or plasma derivatives. The risk assessment would aid the CJD Incidents Panel in assessing the potential risk to individual recipients of blood/components or plasma derivatives subsequently found to have contained a donation from someone who had gone on to develop vCJD.

30. The committee agreed that although there were limited data to support the assumptions made in the risk assessment, at present, they were satisfied with the approach and assumptions adopted by DNV Consulting. The committee provided comments for the revision of the report to the CJD Incidents Panel.

Transmission of prion diseases by blood transfusion

31. In September 2002, the committee considered research by Hunter *et al* (2002)[2], on the transmission of TSEs by blood transfusion from TSE-susceptible sheep of genotype ARQ/ARQ, either experimentally infected with BSE or naturally infected with scrapie. Cases of BSE and scrapie transmission were reported in animals that received whole blood taken from infected donor sheep prior to clinical onset of disease. Since this paper had been published, two further sheep had succumbed to BSE. One of the animals had been transfused with buffy coat (containing white cells only), while the other had been transfused with whole blood.

[2] Hunter N, Foster J, Chong A, McCutcheon S, Parnham D, Eaton S, MacKenzie C, Houston F. Transmission of prion diseases by blood transfusion. J Gen Virol. 2002 Nov;83:2897-905.

32. This work demonstrated that disease transmission via blood could occur, though the committee concluded that this did not provide direct evidence of transmission to humans but there remained a theoretical risk for human health from the transfusion of blood or blood products. The committee agreed that targeted fractionation studies to determine which fractions contained infectivity and whether it varied throughout the incubation period would be very informative.

Public consultation on:
a) Death Certification and Coroners' Services,
b) Removal, Retention and Use of Human Organs and Tissues

33. In August 2002, the Home Office and the Northern Ireland Courts Service commissioned an independent review of death certification and coroners' services in respect of England, Wales and Northern Ireland[3]. The main aim of the review was to create new death certification and investigation systems that served the needs of the public, were adaptable to change, gave bereaved families better rights and provided better support to professional workers within the systems. The Department of Health (DH) and the Welsh Assembly Government also issued a separate consultation document on the legislation relating to human organs and tissues in England and Wales[4].

34. In September 2002, the committee considered both the DH and Home Office consultation reports. The committee had previously expressed concern that the current low post-mortem rate in the elderly might jeopardise public health surveillance for TSEs and inconsistencies in the scope of examinations could affect determination of the cause of death. The committee welcomed the proposal of a new Medical Audit Service, a fully constituted statutory body, which would be responsible for maintaining standards and providing a legislative framework for post-mortem surveillance.

35. The committee noted that the collection of tissue through such surveys would provide valuable information for the surveillance of human TSEs and the quality assurance of diagnostic tests. The committee agreed that the proposed code of practice would help ensure tissue and organs were obtained ethically. The committee did not agree with the recommendation to avoid the import and exports of CNS tissues, as this would hinder the UK collaboration in research and surveillance in the EU and worldwide. The committee responded formally to the consultation and a copy of the response is given at Annex VII.

[3] The Fundamental Review of Death Certification and Coroners' Services. August 2002.

[4] Human Bodies, Human Choices. The Law on Human Organs and Tissues in England and Wales – A Consultation Report. July 2002.

Department of Health annual research report

36. In November 2002, the committee reviewed a research report from DH on CJD epidemiology and surveillance, blood safety, tissue infectivity and strain typing, development and assessment of therapeutic drugs and decontamination of surgical instruments. Updates on progress of the development of a diagnostic test for vCJD and a research plan to investigate the potential infectivity of blood were given.

Revision of ACDP/SEAC Guidance on TSE Agents: Safe Working and the Prevention of Infection

37. In November 2002, the committee commented on the guidance issued by the Advisory Committee on Dangerous Pathogens (ACDP) and SEAC Joint Working Group relating to the safe practices for working with TSE agents in experimental and clinical settings. The committee endorsed the revised guidance on safe working with TSEs, subject to the specified amendments.

Reports from the SEAC epidemiology subgroup

38. The Epidemiology subgroup met in April and September and considered issues including historic butchery practices, epidemiological data on vaccine use, a quarterly analysis of the incidence of vCJD and pre-publication research on abnormal prion protein in appendix and tonsil samples collected in the UK. SEAC endorsed the reports and conclusions of the Epidemiology subgroup at its meetings in June and November.

39. In June 2002, the subgroup updated SEAC on the progress of the investigation into geographically associated vCJD cases. These investigations are conducted jointly by the National CJD Surveillance Unit, the Communicable Disease Surveillance Centre/Public Health Laboratory Service (CDSC/PHLS), the London School of Hygiene and Tropical Medicine (LSHTM) and DH. SEAC concluded that, in contrast to the Leicestershire cluster, no butchery practices had been identified which could be linked with other geographically associated cases. SEAC endorsed the recommendations that further epidemiological data on vaccine use and vaccination history from CJD cases should be collected.

40. In November 2002, the subgroup updated SEAC on:

    - An investigative report on historical uses of Mechanically Recovered Meat (MRM), commissioned by FSA. It was agreed the investigation indicated that around twice as much MRM had come from older adult cattle than had been estimated in an earlier study (10% as opposed to 5%). Members agreed the information contained in the report was very

useful and demonstrated the possible extent to which the population would have been exposed to potentially infected material.

- A paper by Hilton *et al*. (2002)[5] which reported the first positive finding of abnormal prion protein in a retrospective, anonymised study of some 8000 appendix and tonsil samples from patients (aged 10-50 years). The Epidemiology subgroup and SEAC both concluded that the results were of considerable interest, although the prognostic significance of a positive sample was unknown. The committee noted that a prospective collection of 50,000 tonsil samples was to be established, which would enable a much wider study to be undertaken in the future and allow the prevalence of infection to be estimated.

B. Food Safety and the Protection of Animal Health

Intraspecies recycling

41. In June 2002, the committee were asked to advise on the risk of intraspecies recycling from the use of tallow, gelatine, hydrolysed proteins, fishmeal, eggs and egg proteins, milk and milk products and blood within the livestock industry. The committee advised:

    - The risk from tallow was likely to be low, but re-iterated that intra-species recycling should be avoided wherever possible.

    - That the European Scientific Steering Committee (SSC) opinion that the careful sourcing of raw materials in combination with appropriate processing would result in safe gelatine. Therefore, there was no reason to change its earlier view on gelatine derived from ruminant bones and hides.

    - Fishmeal is permitted to be fed to all farmed, non-ruminant livestock, including fish, although to avoid intraspecies recycling, farmed fish should not be fed back to farmed fish.

    - Milk and milk products may be used in animal feed, other than milk derived from clinical cases of BSE. If BSE infectivity should ever be found in milk, the committee would need to re-assess the situation.

[5] Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Penney M, Ritchie D, Ironside JW. Accumulation of prion protein in tonsil and appendix: review of tissue samples. BMJ. 2002 Sep 21;325(7365):633-4.

- The inclusion of blood and blood products in animal feed is banned in the UK. However, under current Animal By-Products Regulations it can be spread on land or incorporated into fertilisers as well as being used in veterinary products. The committee expressed concern over this practice in terms of the potential risk of exposure from use of sheep blood, which could be distributed on fields containing sugar beet where sheep may graze. However, it was recognised that the new EU Animal By-Products Regulations, expected to come into force in early 2003, would place many additional restrictions on blood disposal.

BARB cases

42. In September 2002, the committee was updated on the preliminary epidemiological analyses of the first 17 cases of BSE in cattle born after 31 July 1996. These cases are referred to as BARBs (born after the reinforced ban).

43. It was proposed that imported feed cross-contaminated during transport with mammalian meat and bone meal (MBM) could represent a potential source of infection, as the ban on feeding mammalian MBM in the EU did not take effect until January 2001. In addition, mammalian MBM was imported for the manufacture of pet food, representing another potential source for cross-contamination.

44. The committee acknowledged the cross-contamination of feed was a plausible hypothesis. However, it considered the possibility of maternal and/or environmental transmission being responsible for some cases could not be eliminated on the basis of current evidence. In addition, differences in genetic susceptibility to infection could not be ruled out.

FSA review of the Over Thirty Month Rule

45. The committee were updated in September and November 2002 on the FSA review of the Over Thirty Month (OTM) rule. The OTM rule forbids the sale in the UK of meat from cattle aged over thirty months at slaughter for human consumption. A stakeholder group was set up to advise the FSA on risk management issues, and a risk assessment group considered scientific matters relating to the review. The various options examined by the statistical modelling teams (Imperial College, VLA and DNV Consulting) revealed that changing the OTM rule would result in an increased risk in terms of infected animals entering the food chain. However, given the declining levels of BSE and additional controls, the risks were likely to be very low in comparison to past risk. The committee agreed with the approach taken to assess the risk of changing the OTM rule, but expressed the need to obtain further information on the sensitivity of the diagnostic test for future work.

Historical uses of mechanically recovered meat

46. In November 2002, the committee considered a study carried out by DNV Consulting to establish the main sources of potentially infected material in food during the period of the BSE epidemic. The study focused exclusively on the time period before the main controls on animal feed were implemented (1980 – 1995). Two main sources of potential infectivity were investigated: Mechanically Recovered Meat (MRM), which may have included spinal cord and dorsal root ganglia (DRG); and head meat, due to potential contamination at slaughter. A similar study had reported that the majority of MRM was used in the manufacture of burgers, whereas the DNV Consulting study estimated that similar amounts were used in retail minced meat and burgers.

47. The report demonstrated the extent to which the population would have been exposed to potentially infected material. The committee acknowledged the report provided useful information, but the lack of available documentary evidence on the origin of meat going into the food chain meant there were uncertainties in the results.

C. Research on TSE Issues

Evaluation of the differential diagnostic test for TSEs in sheep

48. In April and September 2002, the committee was updated on progress to develop and validate a modified Prionic Western Blot (WB) rapid test, to discriminate BSE from scrapie in sheep. The VLA had carried out this work. It was reported that the modified WB assay was considered sufficiently robust to allow strain typing in sheep, provided that the test was conducted with care. Statistical analyses demonstrated the mean molecular weights for the unglycosylated prionic band could be used as a discriminatory variable for different strains. The studies confirmed that autolysis could compromise WB results and result in false positives for BSE. Retrospective testing of the scrapie brain samples would commence in October 2002.

49. In its capacity as an EU Community Reference Laboratory, the VLA subsequently received a request from the EU Commission to translate the SSC's 'Strategy to Investigate the Possible Presence of BSE in Sheep' into instructions for all National Reference Laboratories. This would require the development of a common protocol. The planning of the ring trial commenced in September 2002. The committee recommended that a subgroup be set up to review the ongoing work on molecular strain typing and report back to the main committee.

Cattle pathogenesis study

50. In September 2002 the committee received an update from the VLA of a long-term study of the pathogenesis of BSE in cattle. Cattle were orally dosed with 100g BSE infected bovine brain material and culled at various time points after infection and infectivity in tissues detected by cattle bioassay. Previously reported results from the cattle bioassay study had confirmed infectivity in the distal ileum, caudal medulla and spinal cord.

51. One of the five cattle administered with a pooled sample of palatine tonsil taken from animals infected with BSE had shown clinical evidence of onset of BSE at 45 months post-administration. The four remaining animals were alive without evidence of clinical onset of BSE. The committee considered the finding as significant and was unlikely to be an artefactual result. The committee advised that the significance of the tonsil infectivity finding would be strengthened if any of the other four animals in the experimental group developed BSE.

52. Bovine tonsils are specified risk material (SRM) and thus, prevented from entering the food chain from six months of age in the UK but tongue is not classified as SRM. In view of this, the committee recommended that a risk assessment should be carried out to establish the level of exposure to BSE infectivity that the population might be exposed to, based on the results for cattle bioassay of tonsil. A statement produced by the committee on this preliminary result is given in Annex VIII.

Effect of oral dose on attack rate and incubation period in cattle

53. The committee receive regular updates on a Defra funded project investigating the oral dose-response for bovine infected brain material on the attack rate and incubation period of BSE in cattle. In November 2002, the committee was informed that a animal challenged with 0.1g infected brainstem homogenate succumbed to BSE at 50 months post oral dosing. A number of other animals in this dose group showed very early signs of possible disease; however no further cases were confirmed.

Determination of abnormal prion protein in milk

54. In November 2002, the committee was asked to comment on a proposal from the FSA to assess the presence of BSE prion in the milk of cattle experimentally infected with the BSE agent. The committee agreed on the development and validation phase of the proposed analytical methods that would be used. The committee reiterated that the research relating to milk should be a key priority, as it was a product derived from older animals that

were not subjected to the OTM rule. The committee agreed that the formation of a subgroup to advise the FSA might help to facilitate research in this area.

D. TSEs in Sheep

NSP working group report

55. In April 2002, the committee considered conclusions of the National Scrapie Plan (NSP) working group, which had met in March 2002. The committee agreed with the working group's report that:

- The scientific basis of the NSP was sound.
- It was not appropriate to delay the NSP until outstanding questions on issues such as carrier status and mechanisms of TSE transmission had been formally resolved.
- A twin-track approach was appropriate where research to inform policy ran parallel to the implementation of the scheme.
- Action to remove susceptible animals from scrapie-infected flocks would reduce the theoretical risk to public health.
- The preliminary proposal on a certified flock scheme[7] was consistent with the aims of the NSP and would be a useful parallel scheme.

56. In April 2002, some aspects of the NSP needed to be taken forward as a matter of urgency, and the working group reviewed SEAC's advice of February 2001 on the safety of sheep entering the food chain, should BSE ever be found in sheep. The committee noted the conclusions of the working group and agreed that:

- Only animals carrying the ARR allele should enter the food chain.
- On a precautionary basis, the previous SEAC advice of a 12-month age restriction on animals entering the food chain remained appropriate for ARR heterozygotes. However, in view of existing SRM regulations, there was no justification for an age restriction on ARR homozygote animals.
- Only milk from ARR homozygous sheep could be considered as highly unlikely to contain infectious material. Further research was required

[7] The preliminary proposals on a certified flock scheme would allow farmers who had implemented breeding and management strategies to have their flocks certified if an appropriate level of genetic resistance to scrapie was reached.

before potential risks from milk from goats and semi-resistant or susceptible sheep could be excluded.

57. The committee recommended that work to examine possible carrier status in scrapie-resistant sheep should be a primary research objective in relation to the NSP. Research should also be conducted on possible gene loci that may confer resistance to scrapie in goats.

Sheep surveillance meeting report

58. In April 2002, the committee considered a report from a Defra working group on TSE surveillance strategies to gauge the prevalence of scrapie infection in UK sheep. The working group report recommended the use of an inverse sampling regime. This required the testing of a large number of animals (n= 600,000) to generate 600 positive cases. This regime required ten times more than that required under EU rules, which specified the UK must test 60,000 sheep in abattoirs and 6000 in fallen-stock. The committee agreed the EU requirement to test 60,000 sheep would provide a reasonable sample size to assess the current prevalence of TSE in the UK flock and would also provide information on genetic profiles. However, the EU sample requirements were not thought to be adequate to evaluate any subsequent changes in TSE prevalence as a result of the current action to reduce and eliminate scrapie under the NSP.

59. The committee advised that further surveillance to examine the overall prevalence of TSE in the sheep flock, and to explore if BSE was present in UK sheep, was a high priority.

Susceptibility of New Zealand sheep to TSE infectivity

60. In November 2002, the committee reviewed preliminary research funded by Defra to investigate the possible effect of PrP genotype on susceptibility to TSE infection. The study had shown that transmission of BSE to a sheep of the ARR/ARR genotype (considered to be naturally resistant to TSEs) was possible following intracerebral (ic) challenge with BSE-infected bovine brain homogenate. However, the incubation period was approximately twice the average incubation period of 556 days reported in a BSE susceptible genotype (ARQ/ARQ) similarly challenged with BSE infected material in the same study. Previous studies indicated that ARR/ARR sheep were not susceptible to challenge with BSE by the oral route.

61. The committee considered that the resistance of ARR/ARR sheep to TSE infection was not absolute, because the transmission of BSE can occur following ic challenge. However, the committee noted that the oral route was the most likely natural route of the introduction of BSE into a sheep

population. A statement issued by SEAC on February 2003 is given in Annex IX.

E. Reviews

Science in Defra – implications for the management of TSE research

62. In September 2002, Defra's Chief Scientific Advisor (CSA) presented his response to the review of Defra-funded research and surveillance on TSEs to the committee.

F. Committee Business

Open meetings

63. In September 2002, SEAC commenced holding meetings in public.

Annex I

Abbreviations

ACDP	Advisory Committee on Dangerous Pathogens
BARB	BSE case Born After the Reinforced mammalian meat and bone meal Ban
BSE	Bovine Spongiform Encephalopathy
CJD	Creutzfeldt Jakob Disease
CNS	Central Nervous System
COP	Code of Practice
CDSC	Communicable Disease Surveillance Centre
CSA	Chief Scientific Advisor
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
DRG	Dorsal Root Ganglia
EU	European Union
FSA	Food Standards Agency
GB	Great Britain
LSHTM	London School of Hygiene and Tropical Medicine
MAFF	Ministry of Agriculture Fisheries and Food
MBM	Meat and Bone Meal
MRC	Medical Research Council
MRM	Mechanically Recovered Meat
NCJDSU	National CJD Surveillance Unit
NHS	National Health Service
NIBSC	National Institute of Biological Standards and Control
NSP	National Scrapie Plan
OTM	Over Thirty Month
OTMS	Over Thirty Month Scheme
PHL	Public Health Laboratories
PrP	Prion Protein
SEAC	Spongiform Encephalopathy Advisory Committee
SRM	Specified Risk Material
SSC	Scientific Steering Committee
TSE	Transmissible Spongiform Encephalopathy
USA	United States
vCJD	Variant Creutzfeldt Jakob Disease
VLA	Veterinary Laboratory Agency
WB	Western Blot

Annex II

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 Agriculture, Fisheries and Food and the Secretary of State for Health:

Signature:

Name:

Date:

Signed:

Members name:

Date:

Up to date information on Members indemnity can be found on the Defra Website: http://www.Defra.gov.uk/animalh/bse/bse-science/level-4-seac.html

Annex III

Register of Members' Interests at 30 December 2002

SEAC Member	Commercial interests		Non-commercial interests	
	Name of organisation	**Nature of interests**	**Name of organisation**	**Nature of interest**
Professor P G Smith	None	None	Department of Health	Grant holder
Professor A Aguzzi	Boehringer Ingelheim	Occasional consultancy	Swiss National Foundation No: 31-36059.92 3100-040827.94	Principal investigator
	Abbott Laboratories (Chicago)	Support of some laboratory costs e.g. care of mice, instrumentation	Cancer league of the Kanton Zurich	Principal investigator
	Immuno A G (Vienna)	Support of some laboratory costs e.g. care of mice, instrumentation	Eurpoean Union No. BMHI-CT93-1142	Co-investigator
			National Institute of Health	Co-investigator
			Swiss National Research Program NFP38 & NFP38+	Principal investigator
Professor. R Anderson	Decode	Scientific Advisory Board	The Welcome Trust	Governor
	SKB	Scientific consultancy	Tropical Health and Education Trust (THET)	Trustee
	Abbott Pharmaceuticals	Scientific consultancy	London School of Hygiene and Tropical Medicine	Court of Governors
		Non Exec. Chairman	Hamburg Institute of Tropical Medicine	Scientific Advisory Board

			Isaac Newton Institute, Cambridge	Scientific Advisory Board
			Maxwell Institute, Edinburgh	Scientific Advisory Board
Professor C J Bostock (Appointed as an expert from the Institute for Animal Health (IAH), a Biotechnology and Biological Sciences Research Council sponsored institute)	Safeway	Share holding	The UK and some overseas Governments	Research contracts with IAH
			Non-governmental organisations and companies, spanning a wide range of interests including food, agriculture, chemicals and pharmaceuticals. Further details of customers of IAH can be found on the Institute's website (www.iah.bbsrc.ac.uk)	Research contracts with IAH
Professor G Bulfield	British Biotech plc	Share Holder	Share Holder	Director & Chief Executive
	Roslin Bio Centre	Chairman	SHEFC Research Policy Advisory Committee	Member
	B&K Universal Ltd	Non-executive Director	Home Office Animal Procedures Committee	Member
			Advisory Board of Partnerships UK Ltd	Member
			BBSRC Strategy Board	Member

Professor J Collinge	None	None	Welcome Trust	Research grant holder
			Dept of Health	Research grant holder
			European Commission BIOMED programme	Research grant holder
			Medical Research Council	Unit Director and Research grant holder
			Motor Neurone Disease Assoc	Chairman, Research Advisory Panel
			Glaxo Welcome PLC	Research collaboration
			World Health Organisation	Ad hoc Advisor
Professor J Ironside	Merck, USA	Temporary Advisor	Baxter Healthcare USA	Research investigator on a Baxter funded project on the transmission of CJD (Principal investigator Dr Paul Brown USA)
			Department of Health	Research grant holder: Surveillance of CJD (neuropathology) DoH 1216469 - National retrospective review of CJD and respective disorders DoH 1216982 - Immunocytochemical testing for disease-associated prion protein in lymphoid tissues Advisor: Decontamination of surgical instruments Assessment of risk of exposure to vCJD: infectivity in blood and blood products
			Medical Research Council	Grant holder: G9708080 - Edinburgh HIV brain and tissue resource G9627376 - Phenotypic variation in CJD, a clinical pathological and molecular study
			BBSRC	Grant holder: 15/BS204814 - Neuronal pathology in CJD: an immunocytochemical study with quantitative and microscopic analysis

				201/BS410537 - The relationship between neurone damage and clinical disease: relating murine and ovine scrapie to BSE and CJD Advisor: BSEP
			European Union	Grant Holder: EC BI04-98-6046 - Diagnosis of TSE using PrP^{SC}/PrP^{C} EC CT98-6015 - European centralised facility for human transmissible spongiform encephalopathies (prion disease) EC PL97-6003 - Transgenic mice expressing human prion protein. Use for characterisation of human encephalopathies and sensitivity for detection of infectivity EU CT98-6048 - Quantitative analysis of MR scans in CJD (QAMRIC) Advisor
			Committee on safety of medicines	Advisor
			World Health Organisation	Advisor
			UK Xenotransplantation Interim Regulatory Body	Advisor
Peter Jinman			British Veterinary Association	Vice President
Professor H Kimbell	Bass Plc	Small share holding		
	Tesco's Plc	Small share holding		
Professor C Masters	Merck	Consultant	National Health and Medical Research Council of Australia	Principal and Associate investigator

			Several research grants	
	PRANA Biotechnology Plc	Director	World Health Organisation	Occasional consultancies on CJD
			Australian Government	Occasional consultancy on CJD and Director of the National CJD Registry
Professor I McConnell	Marks & Spencer	Veterinary consultant on occasional basis	Welcome Trust	Fellowship holder Research grant holder Panel member for Veterinary Interest Group
			BBSRC	Research grant holder
Dr J Safar		Dr Safar has no commercial interests but according to the intellectual property policies of the University of California (UC) is entitled to a portion of income when UC licences to a commercial entity any patents on which he is named as an inventor.	National Institute of Health, Grant # AGO-10770	Co-investigator
			World Health Organisation	Advisor
			Swiss National Research Programme	Advisor
			Medical Research Council	Advisor
			Non-governmental organisations and companies	Research contracts with UCSF
Professor R Carrell	Canterbury Scientific	Director and Shareholder	Wellcome Trust	Research
Dr D Cunningham	None	None	Standing Medical Advisory Committee	Chair

Annex IV

Membership of the SEAC Epidemiology Sub-Group on vCJD at 31 December 2002

Chairman:

Dr N Gill
PHLS Communicable Disease
Surveillance Centre

Professor PG Smith
Department of Infectious and Tropical Diseases
London School of Hygiene and Tropical Medicine.

Professor R M Anderson
Department of Infectious Disease Epidemiology
Imperial College School of Medicine

Dr S Bird
MRC Biostatistics Unit, Cambridge

Professor J Collinge
St Mary's Hospital

Mr S N Cousens
London School of Hygiene & Tropical Medicine

Professor A Hall
London School of Hygiene and Tropical Medicine

Professor C J Bostock
Institute for Animal Health

Dr R Eglin
National Blood Service

Professor N Day
Institute of Public Health Service
University of Cambridge

Dr G Medley
Department of. Biological Science
University of Warwick

Professor R G Will
National CJD Surveillance Unit
Western General Hospital
Edinburgh

Dr H Ward
National CJD Surveillance Unit
Western General Hospital
Edinburgh

Professor J Wilesmith
Epidemiology Department
Veterinary Laboratories Agency

Dr C P Farrington
Faculty of Mathematics and Computing, The Open University

Annex V

Membership of the SEAC Sheep subgroup to discuss issues relating to the National Scrapie Plan (NSP) at 12 December 2002

Chairman:

Professor PG Smith
Department of Infectious and Tropical Diseases
London School of Hygiene and Tropical Medicine.

Professor A Aguzzi
Institute of Neuropathology,
University of Zurich.

Professor C J Bostock
Institute for Animal Health

Professor R Carrell
Professor of Haematology
University of Cambridge

Professor I McConnell
Institute of Public Health Service
University of Cambridge

Mr P Jinman
Private Veterinary Surgeon

Annex VI

Membership of the SEAC/ACDP Working Group at 31 December 2002

Chairman:

Professor D J Jeffries
ACDP member

Dr M Painter
Consultant in Communicable Disease Control

Professor J Ironside
National CJD Surveillance Unit

Mr B Clare
Director
Bob Clare Associates

Dr P Jones
Institute for Animal Health

Dr T Wyatt
Consultant Clinical Scientist

Ms Dee May
Royal College of Nursing

Dr D M Taylor
Retired-previously at the Institute for Animal Health Neuropathogenesis Unit

Professor P G Smith
London School of Hygiene & Tropical Medicine

Mr R Bradley
Private BSE Consultant

Dr J Hope
Institute for Animal Health

Mr J Richards
Unison

Dr G Ridgway
University College hospital

Dr R Salmon
PHLS Wales

Annex VII

Your reference:
Our reference:

Ms S Osborn
The review of the Coroners' Services
100 Pall Mall
St James
London
SW1Y 5HP

21 November 2002

Dear Ms Osborn

Public Consultation on Death Certification and Coroners' Services

At its meeting on 11 September 2002 the Spongiform Encephalopathy Advisory Committee (SEAC) considered the Home Office consultation report on Death certification and Coroner services. My response is on behalf of the Committee.

SEAC is supportive of the recommendation that change shall be fundamental and have the aim to create new investigation systems, particularly where they enhance public health surveillance. SEAC is concerned that, under present arrangements, if a disease causing dementia is part of the medically certified cause of death, there is a low probability that a post mortem examination will be conducted. We are concerned the prevailing attitude of coroners is not to allow pathologists to validate the cause of a dementia at post mortem and of the reports of inconsistency between coroners in the UK in deciding whether to request a post-mortem and in the depth of examination to determine the actual cause of death. We acknowledge that the low number of pathologists has contributed to the problem and that it might also be due to a lack of resources in this field of enquiry.

We agree with the comment in the Home Office consultation paper that "There is no public authority tasked and resourced …to ensure that deaths which should be referred for further investigation are being properly referred." (para 26). We also support the proposal to examine "individual cases in more depth." (para 27.2)

We emphasise the value of a full post-mortem examination in relation to surveillance of TSEs. As a minimum requirement, this could entail strategic

sampling of the brain. We welcome the proposal on the possible creation of a new Medical Audit Service in which a medical auditor would become responsible for dealing in the first instance with deaths where the main issue appears to be investigation of the cause of death. We agree that the medical auditor should have "the power to decide the purpose and scope of further medical investigation, including scrutiny of existing case notes and/or ordering post-mortems." In our view this might be a useful tool to enable sampling to be done for surveillance purposes, extending wider than CJD (paras 26-37)

- We welcome the consultation paper proposal that a new Medical Audit Service becomes responsible for dealing with deaths where the main issue appears to be investigation into cause of death (para 29.1)
- We agree that the medical auditor should have "the power to decide the purpose and scope of further medical investigation." (para 29.2)

SEAC supports the proposal to develop a national protocol governing the use and arrangements for post-mortems for coroners and/or medical auditors after consultation with expert and family interests. Members of the Committee also agree that the national protocol should stipulate that a coroner should be required to justify why a post-mortem should not be undertaken (Chapter 3 – Post-Mortems para 54)

- SEAC agrees with the view that "Protocols to deal with the verification of death appear to have significant advantages." (para 44)

The Committee stresses the importance of systematic disease surveillance of human prion diseases in order to control these diseases in the population, and to protect public health. We stress that without surveillance and specialist laboratory techniques, it would not have been possible to identify the emergence of vCJD. Furthermore, for a rare disease such as vCJD, which can be difficult to identify at an early stage, and which may possibly be masked by other neurological conditions with similar symptoms in older people, good surveillance requires not only reporting by clinicians, but also confirmation of diagnosis by post mortem examination wherever possible. (Scale and Purposes of Coroners Post Mortem**s** (paras 53-61)**)**

- *We support the view of the consultation paper that "the post-mortem is a recognised and proven source of knowledge on disease prevalence…although there are no systematic processes for capturing this information from coroners' post-mortems and using it beyond the individual case."* (para 58)
- *We concur with the view that some families have a strong urge to know the cause of death of a family member and would like to have a right to request a post-mortem.*

- *SEAC agrees "that it is ageist to assume that there is no point in definitively establishing the medical cause of death in old people."* (para 58). *This is also not in the best interests of public health.*

We wish to reiterate concerns that the public health surveillance of CJD is compromised because of the low numbers of post-mortems conducted in the elderly. We are also concerned about the depth of current investigations to determine what constitutes a "cause of death". (Scale and Purposes of Coroners Post Mortems (paras 53-59)). SEAC endorses the review observation that "there are no systematic processes for capturing this information (disease prevalence) from coroners' post-mortems and using it beyond the individual case." (para 58). We agree that considerate and sensitive explanation of the purpose of hospital post mortems, which emphasise the importance of public health surveillance programmes, will help reduce resistance by families to post-mortem In our view in some instances, there may be forcible public health arguments for conducting a post-mortem even without consent from surviving relatives (para 59-61)

The Committee welcome the opportunity to respond to this consultation. We endorse the clear recognition given throughout the consultation document to the need to involve patients and their families in decision-making processes, and to keep them fully informed. We agree however that the ultimate decision to hold a post-mortem should remain with the coroner or medical auditor taken on public interest grounds, and do not consider consent is an essential pre-requisite. This does not, of course, preclude the importance of providing appropriate information to the patients and families concerned. We consider it important that any new legislation or guidance strikes an appropriate balance on these issues.

Please let me know if the Committee can be of further assistance.
Yours sincerely,

Professor Peter Smith CBE

Chairman, SEAC

Annex VIII

SEAC STATEMENT ON INFECTIVITY IN BOVINE TONSIL

Background

Research results

1. The Committee considered unpublished data on a long term pathogenesis study in cattle. Cattle were orally dosed with 100g of BSE infected bovine brain material. At various times after oral dosing, cattle were sacrificed and different tissues tested for infectivity.

2. In the first instance, infectivity was detected by intracerebral injection of mice (mouse bioassay). Using this assay, infectivity was detected in a few tissues prior to onset of clinical signs:

- distal ileum (the earliest infectivity being detected at 6 months post oral dosing)
- brain and spinal cord (infectivity being detected during the months just prior to the onset of clinical symptoms in cattle)

   However, in a large number of other tissues, no infectivity was detected.

3. It was recognised that intracerebral injection of bovine material into mice involved crossing a species barrier. Later work showed that intracerebral injection in calves (cattle bioassay) was several hundred-fold more sensitive with respect to the detection of putative infectivity in bovine tissues. Therefore, a range of cattle tissues were re-assayed using the more sensitive cattle bioassay.

4. Results from the cattle bioassay study confirmed infectivity in the distal ileum, brain and spinal cord at similar times in the incubation period, as compared with the mouse bioassay. However, a new unpublished finding was presented to the Committee on 11 September. The Committee was informed that in a group of five cattle (recipients), which had been intracerebrally injected with a pooled sample of palatine tonsil, one cow had succumbed to BSE at 45 months post oral challenge. The inoculum (palatine tonsils) had been collected from cattle at 10 months post inoculation. This finding was subsequently confirmed by histopathological and molecular testing of the brain of the recipient cow. The other 4 animals in the experimental group are still alive (48 months after inoculation), and to date are not showing clinical signs of BSE. The equivalent result in mouse bioassay had been negative.

5. The Committee noted that pevious studies on pooled lymph nodes or spleen taken from naturally infected animals with clinical BSE had not shown evidence of infectivity by cattle bioassay. It was also noted that specific lymph nodes were included in the ongoing experiment, and had so far shown no signs of infectivity; although these cattle had been challenged at a later date.

Consideration of potential public health significance

6. The Committee noted that tonsils from cattle are Specified Risk Material (SRM) from 6 months of age in cattle from the UK and Portugal, and from 12 months of age for other EU States. Tongue is not classified as SRM and therefore can be sold for human consumption. Although palatine tonsil is unlikely to be removed with tongue, there is a possibility that some microscopic lingual tonsil might be present in that part of the tongue removed and intended for human food consumption.

7. The Committee was informed by the Food Standards Agency (FSA) that a limited, preliminary examination showed that no visible lingual tonsil was present on tongue as removed, but the possibility that microscopic tonsillar tissue might be present could not be ruled out. The Committee considered that further work was needed to establish the distribution of microscopic tonsillar tissue in tongues prepared for human consumption. The Committee was informed that such tissue was not detectable if tongue was cut in a particular area. However the Committee was unable to assess the magnitude of any risk as sufficient data on current practices were not available at the time of assessment.

8. The Committee recognised that the risk was likely to be low for several reasons:

- The long incubation period in the one experimental animal that had succumbed to BSE suggested that the level of infectivity was low.
- Tonsil is SRM from the age of 6 months in the UK/Portugal and 12 months in other EU states.
- Depending on the of method of harvesting tongues it is possible that little, if any, microscopic tonsil tissue would be included in tongues entering the human food chain.
- The number of BSE infected cattle entering the food chain is likely to be very small because of existing feed controls and the OTM rule.

9. On the question of whether tonsil should be made SRM from any age, the Committee recognised that this was a risk management issue and beyond their strict remit, but considered that this was an option that should be examined as part of the risk assessment.

Conclusions

Significance of the research findings

10. The Committee considered that although only one of the five animals has so far succumbed to BSE, this finding is significant and unlikely to be an experimental artefact. However, the significance of this finding would be verified by:

- the pending results from the other four animals in the experimental group; which are currently not showing clinical signs of BSE
- or if tonsillar tissue sampled at 6, 18 or 26 months after infection showed evidence of infectivity.

Both these studies are ongoing.

11. The Committee recommended that, in addition to cattle bioassay, further studies on lymphoid tissues from cattle should be carried out, using the most sensitive assays, as these become available. This should include validation of this interim finding by exploring all available techniques to detect PrP^{sc} on both the original tonsil tissue material collected, as well as lymphoreticular tissue collected throughout the pathogenesis study.

Requirement for additional information to inform risk analysis

12. The Committee recommended that a risk assessment be carried out to establish the level of exposure to BSE infectivity that the population might be exposed to as a consequence of the possibility of infectivity in tonsil (timescale?). This risk assessment should include risks associated with both UK and imported meats.

13. It was clear that additional studies would be required to inform the Risk Assessment:

- It is necessary to determine how much microscopic tonsil tissue could be present in tongue harvested for human food consumption
- It is also necessary for the FSA to investigate the uses of tonsils that are not classified as SRM.

Annex IX

STATEMENT ON SUSCEPTIBILITY OF DIFFERENT GENOTYPES IN SHEEP TO EXPERIMENTAL BSE

This statement represents the opinion of a specialist sub-group of SEAC which met on 11th December 2002 to consider this specific issue. The statement will be presented to SEAC on February 11th 2003 for discussion.

Background

1. In 1999, SEAC endorsed a recommendation from the SEAC Sheep Subgroup that a long-term control and eradication plan for TSEs in sheep should be established. The National Scrapie Plan (NSP) was initiated on the basis of this recommendation.

2. The rationale of the NSP is to reduce progressively the prevalence of scrapie infection and therefore the incidence of scrapie disease, with an aim to eventually eliminate the disease from the national sheep flock. This is to be achieved by a targeted breeding programme in which levels of resistance to TSEs in sheep are increased according to defined genotypic criteria. Over a number of years the NSP will ensure that the proportion of TSE-resistance genes increases throughout the (highly stratified) sheep flock.

3. Scrapie has been an endemic disease in UK sheep for more than 200 years. Although, there is no evidence that scrapie is a human pathogen, there is still scientific uncertainty about a possible risk to human health from TSE's in sheep. The possibility remains that some sheep may have become infected with the BSE agent through the consumption of BSE-contaminated meat and bone meal (MBM). In experimental studies it has been shown that BSE can be transmitted to sheep by the oral route. The inclusion rate of MBM in feed for sheep was much lower than for cattle and, generally, exposure of sheep to contaminated MBM would have been much less and most exposure would have been prior to the ruminant feed ban of July 1988.[2] However, had BSE been introduced into the sheep population it might have been maintained by transmission from sheep-to-sheep, like scrapie. Also, it may not have been recognised as the clinical

[2] on inclusion of ruminant derived MBM in concentrate foodstuffs for ruminants (the feed ban).

signs of experimental BSE in sheep appear to be the same as those of scrapie.

4. The studies conducted to date, including studies of strain-typing of scrapie cases, do not provide evidence that BSE is present in the sheep population. However as a theoretical risk remains, a dual aim of the NSP is to protect against the theoretical risk of BSE through inclusion of the BSE-resistant genotypes in the breeding programmes for scrapie resistance.

5. Susceptibility to natural infection with scrapie and to experimental infection with BSE varies according to the genotype and breed of the sheep. The underlying principle of the NSP is the premise that the ARR allele confers resistance to TSE's. Previously, this Sub-group has recommended that if new research emerges which indicates that sheep genotypes originally considered to be resistant to scrapie and BSE (e.g. ARR/ARR) were able to incubate disease, the National Scrapie Plan should be reviewed.

Research Findings

6. The views of the SEAC Sheep Sub-group were sought on unpublished results from an ongoing study at the Institute for Animal Health in the UK. This study is funded by Defra. The study was set up to examine further the susceptibility of different sheep genotypes to experimental BSE and scrapie, using intracerebral inoculation, one of the most efficient means of transmitting these agents.

7. Previous studies have indicated that sheep with the genotype ARR/ARR are not susceptible to challenge with BSE, by the oral route. However, the new research reports the experimental transmission of BSE to ARR/ARR sheep following intracerebral challenge with 0.5ml 10% BSE-infected bovine brain homogenate. The incubation period of disease is approximately twice the average incubation period of 556 days reported in BSE susceptible genotypes (ARQ/ARQ sheep) challenged by intracerebral inoculation with BSE in the same study. Apart from a single unconfirmed and disputed case of naturally occurring scrapie in Japan, this is the first report of a TSE infection in ARR/ARR sheep.

Conclusions

8. Members of the Subgroup were asked to consider if this research had implications for the susceptibility of ARR/ARR sheep to TSEs by natural routes of exposure.

9. Members agreed that the transmission of BSE following intracerebral inoculation shows that the resistance of ARR/ARR sheep to TSE infection

cannot be regarded as absolute. They noted, however, that intracerebral inoculation is not a natural route of transmission and had BSE been introduced into the sheep population the most likely route of exposure was oral. Members noted that to date there have been no cases of TSE-related disease in ongoing studies in which ARR/ARR sheep have been orally challenged with BSE. Members agreed that, although the new findings did not establish that BSE could be transmitted to ARR/ARR sheep by natural routes of infection, the possibility could not be excluded.

10 Members noted that ARR/ARR sheep appeared to be highly resistant to infection with scrapie by natural routes, as judged by the absence of cases of scrapie in such sheep. It was noted that very few ARR/ARR sheep had been challenged in experimental studies by intracerebral inoculation of scrapie and their susceptibility to such challenge was unknown. Members also noted that a high proportion of sheep with scrapie susceptible genotypes had developed BSE following experimental oral challenge, confirming the relative resistance of sheep with the ARR/ARR genotype to TSE agents in general.

11. Members acknowledged there were possible parallels with work on experimental TSE's in pigs. In these experiments, transmission of BSE infection had occurred after BSE-infected material had been inoculated intracerebrally combined with other routes. However infection was not established when similar doses of BSE-infected material were fed to pigs. Members agreed, however, that it would be unwise to give undue weight to this parallel observation in interpreting the significance of the new findings in sheep.

12. Members agreed that these new research findings in sheep did not alter the validity of the basic strategy of reducing the prevalence of genotypes susceptible to TSEs as part of the animal and human health case for reducing the prevalence of TSE infections in sheep.

Assessment of the scientific implications for the National Scrapie Plan

13. The scientific rationale for the NSP is to reduce and eliminate the prevalence of any TSE's in sheep. The eradication plan is based on selective breeding to eliminate susceptible genotypes while increasing the prevalence of resistant genotypes (ARR/ARR) in the national flock. Therefore, the general principle underlying the NSP is the premise that the ARR allele confers resistance to TSE's.

14. Members agreed this new research shows that although ARR/ARR sheep are not completely resistant to BSE infection, this genotype is relatively more resistant than other genotypes examined in the NSP. This is evident

from on-going work with orally BSE challenged ARR/ARR sheep. These animals remain healthy five years post challenge whereas ARQ/ARQ animals succumbed by 3 years post challenge.

15. They concluded that although this research shows that ARR/ARR may not be fully resistant to infection, increasing resistant alleles in the national flock would reduce the potential sources of infection and thus reduce the incidence of clinical disease. This would have the ultimate effect of reducing the possibility of potential human exposure to BSE infectivity via the food chain. Members agreed this latest research is a significant development but they did not consider that the new research undermined the scientific basis of the NSP.

16. Members reiterated previous opinion that the issue of carrier states remains a key uncertainty with regard to scientific justification for the NSP. The theoretical possibility remains that ARR homozygous sheep could act as sub-clinical carriers of TSE infection, capable of maintaining and transmitting infection. If resistant sheep proved to be latent carriers of infection then this may impede elimination of TSE infections via the current breeding strategy. Members acknowledged that the new findings do not directly inform this issue, although they noted that research was in progress to address this. Members suggested that consideration be given to testing tissues from any ARR/ARR sheep surviving at the end of the study for evidence of sub-clinical BSE infection. Members agreed this important scientific issue needs to be kept under constant review to ensure the success of the NSP.

17. Members recommended that continued research was required to understand the biological basis of the genotypic differences in susceptibility to TSE infection.

18. Members noted there were insufficient data on other routes of challenge for TSE's to allow comparison with, or to aid interpretation of, experimental studies on scrapie and on BSE. They recommended that additional experiments be conducted to investigate different routes of challenge for both scrapie and BSE (i.e. peripheral routes of exposure for BSE and ic challenge for scrapie).

Annex X

SEAC Secretariat Addresses:

SEAC Secretariat
Area 108
1A Page St
London, SW1P 4PQ

Tel: +44 (020) 7904 6267
Fax: +44 (020) 7904 6827

Email: SEACsecretariat@seac.gsi.gov.uk

For further information on the work of SEAC and its sponsoring Departments: -

SEAC homepage:
http://www.seac.gsi.gov.uk

Defra homepage:
http://www.defra.gov.uk/defrahome.asp

DH homepage:
http://www:open.gov.uk/doh/dhhome.htm

FSA homepage:
http://www.foodstandards.gov.uk