



ANNUAL REPORT 2003

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Foreword

I am pleased to present this, the seventh Annual Report of the Spongiform Encephalopathy Advisory Committee (SEAC) covering the period 1 January 2003 to 31 December 2003. Over the past year, SEAC has considered a wide range of issues.

The committee has considered epidemiological evidence showing that the BSE epidemic in cattle continues to decline. Also the vCJD epidemic is no longer be increasing at the rate seen previously. The committee has also considered risk assessments on possible infection from consumption of ox tongue and associated tonsil tissue, from the use of some mammalian material in medical devices and the possibility of secondary infection arising from the use of bone products for revisionary hip replacement. Other areas the committee considered included TSEs in sheep, a review of the use of cattle bone in food production, the possible origins of BSE cases Born After the Reinforced Ban (so called BARB cases) and studies examining changes to the Over Thirty Month Rule as well as research sponsored by Defra, DH and FSA.

The work of the committee continues to invoke much public interest and the public is welcome to observe the committee at work by attending open meetings. This gives members of the public the opportunity to observe the work of the committee at first hand, providing an excellent insight into how government procures independent scientific advice.

As always, I am very grateful to the committee members who have given their valuable time to consider and 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 Roy Anderson, Dr Deirdre Cunningham, Professor Colin Masters and Dr Jiri Safar all of whom left the committee during this period. I would also like to thank the SEAC secretary and secretariat who supported the committee throughout the year.

The committee continues to be reliant upon access to early research findings and I would like to thank those who throughout the year have helped the committee by presenting these valuable data.

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), Devolved Administrations, and the Food Standards Agency (FSA) 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 had its inaugural meeting on 1 May 1990 and since then has advised the government on matters 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. 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 Food Standards Agency to consider SEAC's advice when formulating public and animal health policies and to publish the advice from SEAC.
6. Committee discussions can include the following:
 - specific requests from Government Departments and officials for advice
 - results 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 from September 2002 the public was invited to observe the committee at work by attendance at the open meetings.

8. The committee publishes much of its work on the SEAC website (www.seac.gov.uk), including agendas, meeting papers, minutes, annual reports and statements. Contact details for the secretariat are also available on the website so that queries can be submitted or to register for attendance at an open meeting.
9. There are occasions where certain issues cannot be discussed in open session, such as pre-publication data. These topics are considered in a reserved business session of the committee. Once the information being considered has been published, the committee will release details of the 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 the Chairman and thirteen Members from wide-ranging backgrounds including epidemiology, neurology, neuropathology, veterinary science, genetics, public interest and public health practice.

Professor Peter G. Smith

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 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 James Ironside

Neuropathologist at the National CJD Surveillance Unit, Edinburgh.

Mr Peter Jinman

Private Veterinary Surgeon and President of 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 Ian McConnell

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

Dr. Corinne Lasmezas

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

Dr Jiri Safar

Adjunct Associate Professor in the Department of Neurology at the University of California, San Francisco, USA.

Professor Roy Anderson

Head of the Department of Infectious Disease and Epidemiology, Imperial College School of Medicine, University of London.

Professor Colin Masters

Professor and Head of the Department of Pathology, University of Melbourne, Australia.

Dr Deirdre Cunningham

Public Health and Medical Director of the Southeast London Strategic Health Authority.

Further details on each of the current SEAC Members may be found on the SEAC Website: <http://www.seac.gov.uk/membership.htm>

Code of Practice for Members

12. The committee agreed a revised Code of Practice in July 1999. This contained further 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 Code of Practice incorporates the seven principles of public life identified by the Nolan Committee in their report on Standards in Public Life. In addition to the above, it gives specific guidance on publication of work by SEAC members, conflicts of interest and confidentiality. Copies may be obtained from the SEAC secretariat or can be found on the SEAC Website: http://www.seac.gov.uk/CoP_index.htm

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, at the beginning of each meeting, 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 and website addresses for SEAC and the sponsoring Departments can be found at Annex IX.

Subgroups

16. The Chairman of SEAC can authorise the setting up of ad hoc subgroups to discharge specific tasks. 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 some of the highly specialised issues which require a substantial input from experts in addition to those on the main committee.
18. The SEAC Epidemiology subgroup (Annex IV) was set up in September 1997 to assess the information about the epidemiology of vCJD and develop as far as possible 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.
19. Other subgroups, such as the Sheep subgroup convene on an ad hoc basis as required.

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 (Annex V). The terms of reference for this group are to:
 - 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. The committee met three times between the period 1 January 2003 and 31 December 2003. During this period SEAC reviewed current research within the field of transmissible spongiform encephalopathies, monitored epidemiological data on vCJD and BSE and dealt with requests 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:

vCJD epidemiology

22. The committee was updated at each meeting with information on the number of vCJD cases in the United Kingdom and worldwide. By November 2003, the total number of definite and probable vCJD cases in the UK was 143, of which six cases were alive. All cases that have been tested were methionine homozygous at codon 129 of the prion protein gene. Six vCJD cases had been reported in France and single cases in Ireland, Italy, Canada and the USA.
23. The numbers of onsets of, and deaths from, vCJD per annum were greatest in 1999 and 2000 respectively, and have declined since that time. Statistical analysis of quarterly data on the incidence of vCJD (produced by the Public Health Laboratory Service) suggest a possible peak in the onset of cases and a possible decrease in the incidence of the disease. The committee agreed that these trends were encouraging but considered that it remains premature to conclude that the epidemic has peaked, and that the possibility of future peaks in the epidemic could not be discounted.
24. The committee noted with concern that the autopsy rate for all CJD referrals has declined since 2000 and this trend has continued. Examination of brain tissue during autopsy is crucial for definitive diagnosis of vCJD and sCJD.

Secondary infection risks from bone products

25. In November 2003, the committee considered a risk assessment produced by the National Blood Service (NBS) together with the Department of Health's Economics and Operational Research (EOR) division on the potential transmission of vCJD via implantation of bone. Clinically, the main use of bone is in revision hip surgery, where an existing artificial hip has to be replaced. The assessment looked at the potential risks of secondary transmission of vCJD associated with the use of different human bone products (processed, unprocessed or pooled bone) under different scenarios for vCJD infectivity in bone and prevalence of vCJD in the population.
26. SEAC considered that, in the absence of any experimental data on the tissue distribution of infectivity of vCJD, it is possible that bone may carry infectivity. The committee recommended that infectivity and transmission studies using bone marrow and blood be conducted to assess the comparable infectivity of these tissues and inform a future risk assessment. The committee noted that processing bone reduces the amount of blood and bone marrow, and therefore would be likely to reduce the potential infectivity. However, pooling donations may increase the risk of infection because of the possibility that any one of the multiple donors may be a source of infectivity. Thus, the committee considered that other than reducing the use of bone, the most robust way of limiting any potential risk of secondary transmission of vCJD from bone would be to use processed but unpooled bone where possible.

Revision of ACDP/SEAC guidance on TSE agents

27. In February and November 2003, the committee were asked to comment on updated guidance issued by the Advisory Committee on Dangerous Pathogens (ACDP)/SEAC Joint Working Group (JWG) on safe practices for working with TSE agents. Following amendments suggested by SEAC in February 2003, the committee endorsed the revised guidance on safe working with TSEs in experimental and clinical settings in November 2003. The committee was informed that the JWG had been formally decoupled from SEAC, therefore the committee would not be formally consulted on the remaining parts of the guidance.

Risks associated with medical devices containing ovine and caprine materials

28. In November 2003, the committee considered a survey from the Medicines and Healthcare Products Regulatory Agency (MHRA) on the use of materials of ovine and caprine origin in medical devices. The survey was conducted in the light of new EU regulations that would come into force in 2004. These would require risk assessments to be made on all medical devices that incorporate animal-based materials. The survey had identified 12 types of medical product used in the UK that contained ovine or caprine materials that may present a potential risk of TSE infection. The products were categorised into three groups and assigned a provisional risk level: wool-containing products (low risk), *in vitro* diagnostic reagents (no risk to patients), and vascular grafts (low risk as solely sourced from Australian sheep-Australia has no history of TSE infection in its sheep flock).
29. SEAC agreed that the possibility of transmission of TSEs via exposure of tissues to wool was likely to be remote. In addition, although it was not possible to discount the possibility that TSEs might be present in the Australian sheep flock, the committee agreed there was no evidence that infected sheep were being used to produce medical devices and the risk from infection from use of these devices was, at most, very low. However, SEAC recommended that the risks from these devices should be reassessed if BSE were found to occur naturally in sheep. In addition, the use of any device that would come into contact via open wounds with tissues, which have a high risk of carrying infectivity such as the central nervous system, would have to be reassessed as contact transmission of TSE into open wounds would be a relatively efficient method of infection.

Epidemiology subgroup report

30. The SEAC Epidemiology subgroup met in May 2003. In June 2003, when SEAC received an update from the subgroup, the committee:
 - Noted that the vCJD epidemic was no longer increasing at the rate seen previously and might have reached or be reaching a peak.
 - Agreed with the subgroup's recommendation that the CJD surveillance programme be continued, as the prediction of the evolution of the CJD epidemic in genotypes other than methionine

homozygotes was uncertain and there was the theoretical possibility that there may be clinical manifestations of infection with the BSE agent other than vCJD.

- Endorsed the view of the subgroup that long-term surveillance was important to analyse the number of vCJD cases in the population cohort born in the 1980s.
- Noted that a paper by Ghani *et al*¹ that had projected the future size of the vCJD epidemic after adjusting for the prevalence of abnormal PrP in tonsil and appendix specimens reported by Hilton *et al*², estimated a lower number of vCJD cases than previous predictions.
- Requested an update on future retrospective and prospective studies in appendices and tonsils which aim to provide a better indication of the prevalence of asymptomatic infection of abnormal PrP in the UK population.

B. Food Safety and the Protection of Animal Health

BSE offspring cull

31. In February 2003, SEAC was informed that, in order to meet EU TSE regulations, the UK would need to implement a cull of cattle offspring born at any time after the development of BSE in the dam or offspring born up to two years prior to the onset of BSE in the dam. However, offspring born outside those two years and aged under 30 months could go into the food chain. The committee considered that the available scientific evidence did not suggest that the offspring of BSE cases born more than two years before the onset of BSE in the dam were at higher risk of BSE than the offspring of cattle without BSE. The committee therefore considered that there was no scientific evidence to suggest that the EU regulations would increase the risk of human exposure to BSE infected animals. In addition, consumers would continue to be protected by the ban on feeding mammalian

¹ Ghani AC, Ferguson NM, Donnelly CA, Anderson RM. Short-term projections for variant Creutzfeldt-Jakob disease onsets. *Stat Methods Med Res.* 2003 Jun; 12(3): 191-201.

² 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.

meat and bone meal (MMBM) to all farmed livestock, the removal of specified risk material (SRM) in abattoirs and by the Over Thirty Month (OTM) rule.

BSE epidemiology and Born After the Reinforced Ban (BARB)³ cases

32. In February 2003, the committee was updated on BSE epidemiology in the UK. The data showed that there had been a sharp decline (40%) in the number of BSE cases from 2001 to 2002 and the average age at onset of disease had increased over time. The committee noted that by January 2003, 31 BARB cases had been diagnosed in Great Britain. The committee noted that BARB cases had longer incubation periods compared with earlier cohorts of animals which may suggest that these animals could have been exposed to a lower level of BSE infectivity.
33. By 6th October the number of BARB cases had increased to 59. In November 2003, SEAC discussed the possible origins of BARB cases. The committee noted that the incidence of BARB cases was too high to support the hypothesis of a sporadic occurrence of the disease. The distribution of cases between dairy (46 cases) and suckler (13 cases) herds and the occurrence of two pairs of cases from herds with a previous history of BSE also argued against a sporadic cause. The committee noted that BARB cases were geographically differently and more randomly distributed compared with Born After the Ban (BAB)⁴ cases. Although the difference in geographical distribution of BAB and BARB cases did not support an obvious environmental cause for the BARB cases and was inconsistent with the distribution of contaminated feed from previous suspect sources, the committee considered it important to investigate the origins of feed materials and colostrum fed to BARB cases. It was also considered that maternal transmission and other environmental factors could not be ruled out as possible causes for at least some of the BARB cases. The committee recommended that genotyping, biochemical and strain typing studies should be pursued and an epidemiological case-control study on BARB cases should address

³ BSE cases in the GB born after 31 July 1996 (after the total ban on sale and supply of mammalian meat and bone meal (MMBM) or any feedstuff containing MMBM. These are known as **B**orn **A**fter the **R**einforced **B**an (BARB) cases.

⁴ These are cattle which were **B**orn **A**fter the **B**an on the feeding of ruminant protein to ruminants, which was introduced in July 1988.

the issue of whether colostrum from animals with BSE was a possible source of infection.

FSA Review of the Over Thirty Month (OTM) Rule

34. The committee was updated in February and June 2003 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 30 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. As part of this process, Imperial College and Veterinary Laboratory Agency (VLA) provided epidemiological assessments of the number of BSE infected cattle entering the food chain at different stages in their incubation period. On the basis of the results from this modelling work, the FSA had commissioned DNV Consulting to estimate the potential human exposure through the food chain, by considering the infectivity of the individual tissues concerned.
35. The various options examined by the statistical modelling teams (Imperial College, VLA and DNV Consulting) revealed that changing the OTM rule would result in a very small increased risk of infected animals entering the food chain in GB. The relative effect would be very similar for GB and Northern Ireland. The predicted risk of BSE infectivity from animals imported from the Republic of Ireland would be less than that from UK animals. The committee agreed that given the declining levels of BSE and additional controls, the risks were likely to be very low in comparison to past risk.

Review of the use of cattle bone in food production

36. In November 2003, the committee was asked to advise on the current knowledge on the infectivity of bone and bone marrow in cattle infected with BSE. Current regulations prevent the use of beef bones in processed products, unless the product is sold directly to the consumer from the premises on which it was made. The ban was a precautionary measure introduced because of the possibility that bovine bone marrow might be infective.
37. The infectivity in bone marrow had been reviewed by SEAC in 1998 when the committee considered the results from a mouse bioassay

study of the infectivity of sternal bone marrow from cattle orally exposed to BSE. A single positive result from this mouse bioassay, at 38 months post inoculation, suggested that the level of infectivity was low. However, on the advice of SEAC, infectivity of bovine bone marrow had been examined in a more sensitive cattle bioassay. In November 2003, the committee noted that no clinical signs of BSE in any of the animals in the bioassay had been reported up to 55 months post inoculation. The committee agreed the results from the cattle bioassay indicated that the level of infectivity was at most very low and considered that the single positive finding from the mouse bioassay might be an experimental artefact, but it could not be discounted. The committee agreed that a more detailed study would be needed before a more accurate quantification and analysis of bone marrow infectivity could be made and recommended re-examination of brain tissues from the original mouse bioassay experiment with the new and more sensitive diagnostic techniques.

Risk Assessment of ox tongue and associated tonsil tissue

38. The infectivity of ox tongue and associated tonsil had been previously considered by SEAC in September 2002 when the committee was informed that clinical BSE had been observed in one out of five cattle that had been inoculated 45 months earlier with pooled palatine tonsil from animals orally infected with BSE. At that time SEAC had recommended that further work was required to assess the risk of BSE infectivity from ox tongue, given the proximity of tongue to tonsillar tissue.
39. In June 2003 members were informed that the remaining four animals in the cattle bioassay had no clinical signs of BSE at 58 months post-inoculation. The committee also considered a risk assessment prepared by DNV Consulting on behalf of the FSA, on the risk of BSE infectivity entering the food supply from ox tongue potentially contaminated with tonsil tissue. Included in the risk assessment were results from a study by the VLA that had looked at the amount of residual tonsil tissue on ox tongue and shown that a significant amount of tonsil tissue was present on around half of the ox tongues examined. The committee noted the uncertainty in some of the assumptions made in the risk assessment, particularly with respect to the level of infectivity in tonsil tissue. However, the committee agreed that the potential risk of infectivity from consumption of ox tongue was likely to be very small. A statement issued by the committee on the

BSE risk from bovine tonsil and the consumption of tongue is given in Annex VI.

C. Environmental Issues:

Proposed relaxation of controls on the use of mammalian meat and bone meal (MBM) in fertiliser

40. In June 2003, the committee was asked to advise on whether, in the light of new EU animal by-products regulations, changes to existing UK fertiliser controls would result in significant additional risk to animal health from TSEs. The proposed changes in the UK regulations permitted the use of category 3⁵ mammalian material in compound fertilisers for use on non-pasture land and to allow ash derived from category 2⁶ and category 3 material on land without restriction.
41. The committee considered that the risk of infectivity from ash produced by incineration at temperatures at or above 850°C was likely to be extremely small. In addition, the use of ash produced from the incineration of meat and bone meal (MBM) derived from category 2 and category 3 materials on land without restriction would not result in significant additional risk to animal health. The committee reiterated its earlier advice (in March 1996) that mammalian MBM should not be permitted in fertilisers likely to be spread on agricultural land or land where animals may graze.

⁵ Category 3 is material which is fit for human consumption.

⁶ Category 2 is high risk material (e.g. diseased animals, animals which die on farm and which do not contain SRM at the point of disposal)

D. Research on TSEs

BSE prion propagation in transgenic mice expressing human prion protein

42. In February 2003, the committee considered a study⁷ looking at the neuropathology and molecular properties of PrP in transgenic mice lines (Tg 35 and Tg 45 both of which express the human PrP homozygous for methionine at codon 129) after inoculation with homogenate from BSE infected bovine brain. In the Tg 45 mice, inoculation produced no clinical disease but histological, immunohistochemical and western blot analysis confirmed sub-clinical infection. In addition, the properties of PrP in these tests and the pathology of the disease were similar to those in humans infected with vCJD. In contrast, some of the Tg 35 mice showed clinical signs of infection and tests showed that the PrP in these animals had similar properties to PrP in humans with sCJD. It had been suggested by the authors that these results raised the possibility that some cases of sCJD in humans might be associated with BSE infection. The committee agreed that the detection of sub-clinical disease had important implications. However, although the hypothesis was plausible, further research was required to provide supportive evidence before firm conclusions could be drawn.

Update on DH funded research

43. In February 2003, SEAC was updated on DH funded research on TSEs. The committee was informed that a retrospective survey of tonsil/appendix samples, a prospective study of 5000 tonsil samples, a retrospective survey of atypical dementia, an investigation on progressive intellectual and neurological diseases in children under 16 years of age and a study to determine the exposure of haemophiliacs to vCJD were all ongoing. Additionally, a clinical trial of quinacrine as a treatment for vCJD was planned and a Clinical Trial Steering Committee was currently being set up. The committee was also informed that a plan had been developed by a subgroup of the Committee for the Microbial Safety of Blood and Tissues for Transplantation to facilitate screening of human blood once a diagnostic assay to detect PrP in blood from preclinical cases of CJD

⁷ Asante EA *et al.* BSE prion propagate as either variant CJD-like or sporadic CJD-like prion strains in transgenic mice expressing human prion protein EMBO. 2002; 21: 6358-66

was available. Also, a Science and Engineering Decontamination Group had been established to facilitate the implementation of research findings into practical healthcare settings.

Update on Defra funded research

44. In February 2003, SEAC was updated on the Defra funded research. The committee was informed that studies on the distribution of infectivity (pathogenesis) in sheep infected with scrapie and experimental BSE were ongoing. In addition, the development of diagnostic tests for TSEs remained a major focus of research regarding pre-clinical as well as differential diagnostic tests to discriminate between experimental BSE and scrapie in sheep. SEAC was also informed that work on the nature of TSE strains following serial passage in different species was ongoing. Studies to determine the minimum oral dose in cattle, epidemiological studies on BARB cases and test development to detect ruminant protein in animal feed were also continuing. Research to determine if the National Scrapie Plan (NSP) breeding strategy would affect rare breeds and the commercial viability of progeny would be commissioned.

Joint Funders Group strategy for TSE research

45. In June 2003, the committee welcomed a review of the Joint Funders Group (JFG) strategy for research and development in TSEs. The JFG meet to discuss the research portfolios of each organisation to ensure that research programmes in the TSE field address priority areas, and form the basis of a coherent strategic approach between funding bodies. SEAC was asked to comment on the JFG's draft strategy for research and development in TSEs. Members considered that important research areas included the structure and function of PrP^{Sc}, the mechanism of neurodegeneration, therapeutic strategies for CJD, the development and validation of rapid *in vitro* tests and bioassays in transgenic animals. SEAC noted that the review would be issued for consultation and SEAC would be consulted.

Update on cattle pathogenesis study

46. In June and November 2003, the committee was updated by the VLA on a long-term study of the pathogenesis of BSE in cattle following oral

exposure of calves to a single large oral dose (100g) of homogenate from BSE infected cattle brain. Cattle were culled at various time points after infection and infectivity in tissues detected by bioassays. Clinical signs of BSE occurred first at 35 months post-infection and infectivity was detected by mouse bioassay in the distal ileum, CNS, dorsal root ganglia and trigeminal ganglion. Infectivity studies had been repeated using a more sensitive cattle bioassay which had confirmed infectivity in the caudal medulla, spinal cord, the distal ileum and, in a single animal, in palatine tonsil.

47. In June 2003, the committee noted that one of five cattle inoculated with a pooled sample of lymphoid tissue from the nictitating membranes of naturally infected BSE cases succumbed to disease at 33 months post-infection. However, it was noted that nictitating membrane was not used in the human food supply.
48. In November 2003, the committee was informed that, in a study in cattle using lower doses of infectious material, animals had succumbed to BSE after oral challenges ranging from 0.01-1.0g of bovine infected brain material. In addition, a single animal challenged with 0.001g bovine infected brain material had shown clinical signs typical of BSE.

E. TSEs in sheep

Report from the Sheep Subgroup

49. In February 2003, the committee considered a statement from the SEAC Sheep subgroup, which had met to discuss unpublished results from an ongoing study at the UK Institute for Animal Health. The study was set up to examine the susceptibility of different sheep genotypes to experimental BSE and scrapie following intracerebral inoculation. SEAC endorsed the report of the subgroup pending minor amendments. The statement on susceptibility of different genotypes in sheep to experimental BSE is given in Annex VII.

Research on experimental BSE in sheep

50. In June 2003, the committee was updated on the Defra-funded research investigating the pathogenesis of BSE in sheep after intracerebral inoculation with 0.5mL of 10% bovine BSE brain homogenate. Three out of a total of 19 sheep of the ARR/ARR PrP

genotype developed BSE following the challenge. The incubation period in these sheep was longer than the sheep of the ARQ/ARQ PrP genotype. Only the sheep of the ARQ/ARQ genotype developed disease after oral challenge with a large dose (5g) of BSE infected bovine brain material and exhibited PrP^{Sc} in lymphoid tissues from four months post inoculation. In a Defra-funded study, no vertical transmission⁸ of BSE in sheep of the AQ/AQ, AQ/AR or AR/AR genotype was observed. The committee suggested that if BSE were ever found naturally in sheep the infectivity results for the liver and muscle would be important, as they would help formulation of policy on specified risk materials (SRM).

VLA Survey of sheep tissues

51. In June 2003, the committee was informed about results from the VLA scrapie surveillance programme. In two parallel abattoir surveys, on testing brain samples from sheep using rapid ELISA, a total of 58 positive cases had been detected in nearly 50 000 samples and the results confirmed by immunohistochemistry (IHC). However, a further 28 samples that tested positive for TSE in the ELISA tests could not be confirmed by IHC. It had been suggested that this could have been due to differences in analytical sensitivity between the tests or the differential sensitivity of PrP in individual sheep to Proteinase K used in the ELISA test.
52. There was a disparity in the distribution of genotypes between the abattoir surveys and passive surveillance. The committee agreed that the disparity was due to the fact that the abattoir survey had been carried out on older animals, and had picked up few ARQ and VRQ homozygous animals. In these animals surveillance based on lymphoid tissues may have advantages as PrP^{Sc} tends to be detected in lymphoid tissues first. The committee recommended it would be ideal if both whole brain and lymph nodes could have been examined in all animals.

⁸ Vertical transmission is considered as the spread of infection from mother to offspring during development *in utero*, during birth and/or *via* breast milk.

Scrapie strain typing programme

53. In June 2003, the committee was updated with the progress of a scrapie strain-typing programme carried out by the VLA. Using a modified western blot detection method for TSEs, 770 samples from 1124 suspected scrapie cases were detected positive for TSE in a prospective study. In a retrospective study, started in 1998, 1041 samples from 1062 cases were positive for TSE. The positive samples did not show profiles indicative of BSE in sheep. The committee agreed that the relatively small number of flocks from which the scrapie cases had originated limited the value of these results in terms of whether BSE was in the national flock, but acknowledging this caveat the committee concluded that there was no evidence for BSE in the sheep that had been tested.

Report from expert group on TSE strain differentiation

54. In June and November 2003, SEAC were informed of the conclusions of expert group meetings to consider the progress of the sheep TSE strain differentiation work (ring trial) at the VLA.

55. In June 2003, SEAC was informed that:

- The EU Commission had asked the VLA as the Community Reference Laboratory (CRL) to set up an expert group to investigate the possible presence of BSE in sheep by establishment of ring trials using available rapid TSE tests.
- The expert group would report abnormal findings to national bodies which in turn would report to the advisory bodies and the EU Commission.
- The ring trials would use Western blot, ELISA and CDI (conformation dependent immunoassay) to investigate the effect of sampling different sites in samples of scrapie and experimentally infected BSE. These samples would be issued to participants in the ring trial, together with positive BSE and scrapie tissues and would be tested "blind".

56. In November 2003, the committee:

- Agreed with the expert group's recommendation that samples be collected from brain stem and macerated before testing. Ovine samples, from animals with experimental BSE or natural scrapie, would be used as positive controls.
- Received an update on the scrapie strain-typing programme that they discussed in June 2003. It was noted that 1237 samples from 1280 suspected scrapie cases were positive for TSE in a retrospective study carried out by the VLA. The remaining 43 samples were to be retested due to weak or negative results in the first test. Prospectively 955 (n=1390) animals had tested TSE positive. None of the TSE positive sheep brain samples was positive for BSE.

Defra BSE contingency plan

57. In June 2003, the committee was asked to advise on whether recent scientific developments altered the potential risk of BSE infection with respect to meat from ARR homozygous and ARR heterozygous sheep and milk from ARR homozygous sheep. The committee reiterated its previous advice of March 2002 that should BSE be found in sheep then sheep heterozygous for the ARR PrP genotype less than 12 months of age and ARR homozygous sheep of all ages could be allowed into the food chain. However, only milk from ARR homozygous sheep could be considered as highly unlikely to contain the TSE infectious agent.

Report from expert panel on unconfirmed results in the UK scrapie surveillance survey

58. In November 2003, the committee was informed of the recommendations made by an expert panel, convened by Defra and FSA, to discuss unconfirmed results in the UK scrapie surveillance survey. The survey on scrapie in GB, published by Defra, indicated that the TSE status could not be determined for some sheep (28 out of 29,201 abattoir sheep) because of inconclusive TSE test results from these samples (see paragraph 51). The expert panel agreed it was essential to resolve the discrepant results and recommended that further research should be carried out before any interpretation of these findings could be made. The committee accepted the

conclusion of the expert panel and agreed that the research recommended by the panel should be pursued. A statement issued by the Expert Group on unconfirmed ELISA positive samples in the UK national scrapie survey of cull sheep is given in Annex VIII.

Abbreviations

ACDP	Advisory Committee on Dangerous Pathogens
BSE	Bovine Spongiform Encephalopathy
CNS	Central Nervous System
CJD	Creutzfeldt Jakob Disease
Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
EU	European Union
FSA	Food Standards Agency
GB	Great Britain
MAFF	Ministry of Agriculture Fisheries and Food
NHS	National Health Service
NSP	National Scrapie Plan
OTM	Over Thirty Month
OTMS	Over Thirty Month Scheme
SEAC	Spongiform Encephalopathy Advisory Committee
SRM	Specified Risk Material
TSE	Transmissible Spongiform Encephalopathy
US	United States
vCJD	Variant Creutzfeldt Jakob Disease
NCJDSU	National CJD Surveillance Unit
MRC	Medical Research Council
BARB	Born After the Reinforced Ban cases
BAB	Born After the Ban
VLA	Veterinary Laboratory Agency

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>

Register of Members' Interests at 31 December 2003

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,	Scientific Advisory Board

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			Edinburgh	
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 R Carrell	Canterbury Scientific	Director and Shareholder	Wellcome Trust	Research

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Dr D Cunningham	None	None	Standing Medical Advisory Committee	Chair
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

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				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		
Dr C Lasmezas	Bayer	Occasional consultancy	European Union Framework 5	Grand Holder (4)
			AFSSA	Member of TSE committee and scientific board
			INRA	Member of Scientific board
			INSERM	Advisor to the Scientific board
Professor C Masters	Merck	Consultant	National Health and Medical Research Council of Australia Several research grants	Principal and Associate investigator
	PRANA Biotechnology Plc	Director	World Health Organisation	Occasional consultancies on CJD
			Australian Government	Occasional consultancy on CJD and Director of the National CJD Registry

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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

**Membership of the SEAC Epidemiology Subgroup on vCJD
at 31 December 2003**

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

Membership of the SEAC/ACDP Working Group at 31 December 2003

Chairman:

Professor D J Jeffries
ACDP member

Dr M Painter
Consultant in Communicable
Disease Control

Professor P G Smith
London School of Hygiene &
Tropical Medicine

Professor J Ironside
National CJD Surveillance Unit

Mr R Bradley
Private BSE Consultant

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

Dr J Hope
Institute for Animal Health

Dr P Jones
Institute for Animal Health

Mr Ron Spellman
Unison

Dr T Wyatt
Consultant Clinical Scientist

Dr G Ridgway
University College hospital

Ms Dee May
Royal College of Nursing

Dr R Salmon
PHLS Wales

STATEMENT ON INFECTIVITY IN BOVINE TONSIL

Background

1. The views of the Committee were sought on unpublished results from an ongoing long-term study of the pathogenesis of BSE in cattle. This study is being carried out by the Veterinary Laboratory Agency and is funded by the Food Standards Agency (FSA).
 - In the DNV risk assessment the infectivity in distal ileum, brain and spinal cord was estimated for a fully infected BSE in cattle)
2. Members noted no infectivity was detected in tongue tested by the mouse bioassay.

Research Findings

3. Research from the cattle bioassay study showed in October that one of five cattle that received pooled palatine tonsil tissue, taken 10 months after experimental inoculation with BSE, had shown clinical evidence of the onset of BSE at 45 months post-inoculation. The Committee noted that the other four animals in the experimental group were still alive (48 months after inoculation), with no clinical evidence of onset of BSE.
4. The Committee agreed that even though one of the five animals has shown evidence of transmission of BSE, the finding was significant and was unlikely to result from experimental artefact.

Assessment of potential public health implications

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

6. The Committee had recommended to the FSA that it would be prudent to conduct further examination of current practices of preparing bovine tongue and of the amount and distribution of any tonsil tissue in tongues prepared for human consumption. They were informed by FSA that a more extensive examination of current practices of cutting and removal of the tongue, indicated that visible lingual tonsil was present on tongue as removed.
7. Despite the substantial scientific uncertainty, the Committee considered that any potential risk was likely to be low as the long incubation period of the one animal that had developed BSE (45 months post-inoculation) in this experiment suggested that the level of infectivity was low. Additionally the Committee considered that the potential for exposure is limited given:

The number of BSE infected cattle entering the food chain is likely to be very small because of the decline of the BSE epidemic in the UK, existing feed controls and the over thirty month (OTM) rule.

Tonsil is SRM from the age of 6 months in the UK and Portugal and 12 months in other EU states.

Although the quantity of tonsil tissue attached to tongues is unknown, it is likely, at most, to be small.

8. With respect to bovine lymphatic tissue other than tonsil, the Committee noted that a previous study on pooled lymph nodes or spleen taken from naturally infected animals with clinical BSE had not shown evidence of infectivity by cattle bioassay. The Committee was informed that assay of specific lymph nodes were included in the ongoing experiment and at present have not shown evidence of infectivity, but the assay is incomplete.

Conclusions

The Committee was not able to assess the magnitude of the potential risk, as insufficient information on current practices was available at the time of assessment. In view of this, the Committee made a number of recommendations.

Recommendations

The Committee recommended that a risk assessment be carried out to establish the potential level of exposure to BSE infectivity that the human population might be exposed to as a consequence of the possibility of infectivity in tonsil tissue. The Committee considered that further work was needed to establish the distribution of tonsillar tissue in tongues prepared for human consumption. The assessment should include risks associated with both UK and imported meats. The Committee recommended that it is also necessary to investigate the food uses of tongues and of tonsils from young animals that are not classified as SRM.

The Committee reiterated its previous recommendations in that further studies on lymphoid tissues from cattle should be carried out, using the most sensitive assays, as these become available. These should include validation of this interim finding by exploring all available techniques to detect PrP^{sc} on both the original tonsil tissue material, and tongues for human consumption as any lymphoreticular tissue tested in the mouse bioassay that had not been included in the cattle bioassay.

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 1988.¹ 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 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

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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.

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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).

UNCONFIRMED ELISA POSITIVE SAMPLES IN THE UK NATIONAL SCRAPIE SURVEY OF CULL SHEEP

Expert Panel Group Conclusions from meeting on
Wednesday 17th September 2003

Background

A summary of the results of scrapie surveillance in sheep in Great Britain (Jan 2002-March 2003) was published on Thursday 11th September 2003. The report is available from the Defra web site (www.defra.gov.uk).

This report showed that 28 sheep were positive by the Bio-Rad Platelia assay but these results could not be confirmed by OIE approved confirmatory methods (immunohistochemistry). At Defra's and FSA's request, an expert group was asked to advise on the scientific basis and significance of these inconsistent results. The expert group met on September 17th with the following terms of reference:

- To review the results of the Scrapie Surveillance report and preliminary research conducted by the VLA to investigate possible reasons for the lack of correlation between the Bio-Rad screening test and the OIE confirmatory tests used in this survey.
- To recommend and prioritise further work that should be undertaken to help resolve outstanding analytical issues identified by expert panel.
- To advise on research needed to clarify the biological significance of these findings when they are shown to be analytically interpretable.

The Expert Group included:

- Professor Chris Bostock (Chair) – SEAC
- Dr Martin Groschup – Centre for Virus Diseases of Animals, Germany
- Dr Thierry Baron – AFSSA, Lyons, France
- Professor Guy Dodson – Head of Division of Molecular Structure, NIMR, UK.
- Dr Jean-Philippe Deslys – Head of the Prion Protein Research Group, CEA, France.
- Professor Robin Carrel – SEAC and Department of Haematology, University of Cambridge, UK.
- Professor Jiri Safar – SEAC and Department of Neurology, University of California, USA.

Conclusion of Group

The Scrapie surveillance report identified a number of unclassifiable samples, which showed inconsistent results between different diagnostic tests used to measure the presence of a marker of scrapie infection. The expert group reviewed preliminary research from the VLA carried out to further characterise these samples and received presentations on related research from members of the expert group.

The expert group recognised the importance of these findings but agreed that, due to a lack of data, it was not possible, at this early stage, to draw any firm conclusions about the basis for and significance of the discrepancies reported. The expert group agreed it was essential to resolve this issue and recommended further research that will need to be carried out before any interpretation can be made. This will include comparison of the properties of test reagents, in-depth investigations into the disease marker and epidemiological studies. Infectivity studies in sheep and mice will also be necessary to establish unequivocally whether or not these results are indicative of a sub- or pre-clinical TSE infection.

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