



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE
Draft minutes of the open session of the 87th meeting held on 21st April
2005

At

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

Members:

Professor C. Higgins (Chair)
Mr. J. Bassett
Dr. D. Brown
Dr. J. Chambers
Professor N. Hooper
Professor J. Ironside (Deputy Chair)
Mr. P. Jinman
Dr. C. Lasmezas
Professor J. Manson
Professor I. McConnell
Ms. D. McCrea
Professor G. Medley
Professor M. Stanley

Assessors:

Mr. N. Gibbens (Defra)
Mr. A. Harvey (FSA)
Mrs. E. Lawrence (DH)

DA Assessors:

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

Technical Advisors:

Dr. P. Barrowman (Defra)
Dr. S. Dixon (FSA)
Dr. J. Stephenson (DH)
Dr. D. Matthews (VLA)

SEAC Secretary: Miss K. Richards

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

Also in attendance: Dr. M. Turner (UK Blood Services) for item 3 in morning session.
Mr. P Comer (DNV Consulting) for item 2 in afternoon session.
Dr A. Adkin (VLA)
Mr. S. Wyllie (Defra) and
Mr A. Brewer (Defra) all for item 3 in afternoon session.

DRAFT

MORNING SESSION

ITEM 1 – CHAIR'S INTRODUCTION

1. The Chair welcomed everyone to the 87th meeting of SEAC. He explained to members of the public that it was the Committee's normal policy to conduct as much of its business as possible in open session. Due to the forthcoming general election, and the associated period of 'purdah', some of today's agenda items relating to policy would be discussed in closed session. However, as soon as possible after the election, papers relating to these items would be made available to the public on the SEAC website.
2. The Chair informed members that the current Deputy Chair, Professor Ironside, would be leaving the committee at the end of the month, upon completion of his second term of office. He thanked him for his enormous contribution to the work of the committee. Other members of the committee also expressed their appreciation. The Chair thanked Mr Jinman for agreeing to take over as Deputy Chair from the next meeting.
3. Apologies for absence had been received from Dr Rudge. Professor Stanley was unable to attend the afternoon session.
4. The Chair brought to members' attention that the committee was advertising for two new members, a medical neuropathologist, and a veterinarian with molecular and biochemical expertise. He invited members to encourage suitably qualified colleagues to apply. The closing date for applications is 9 May. Appointments would be made under Nolan rules.
5. The Chair informed members that the one-year trial to evaluate the use of webcasting SEAC meetings had recently been completed. The SEAC Steering Group had decided that, since few people had viewed the webcast live, meetings would continue to be filmed but the meeting would no longer be broadcast live. Recordings would be made available on the SEAC website within two days of meetings and CDs of the recordings would be available about a week after each meeting. Members were content with this proposed way forward.
6. The next SEAC meeting would be held on 30th June 2005 in London.
7. Members were reminded of their obligation to declare conflicts of interest at the start of each agenda item.

ITEM 2 – APPROVAL OF MINUTES FROM SEAC 86 (SEAC 87/1) AND MATTERS ARISING

8. The minutes of the last meeting had been circulated to members, presenters and assessors and some amendments already incorporated. They were agreed as a correct record subject to the following amendments:
- change paragraph 15 line 4 from “...although infection was found...” to “...although PrP^{Sc} was found...”;
 - change paragraph 18 line 6 from “...differentiate strains of PrP agent.” to “...differentiate strains of prion.”;
 - change paragraph 27 lines 14 - 15 from “...oral transmission of BSE between primates.” to “...oral transmission of BSE from cattle to cattle.”;
 - change paragraph 28 by inserting before the final sentence a new sentence: “However, the overall survival time was the same.”;
 - change paragraph 39 3rd and 4th sentences from “Use of hypochlorite was inefficient but laboratory detergents removed some but not all proteins from surfaces. Many of the commercial detergents used in SSDs were relatively efficient.” to “Some laboratory detergents removed some, but not all proteins from surfaces, but many of the commercial detergents used in SSDs were relatively efficient”. The reference to hypochlorite was removed because the data were preliminary; and
 - change paragraph 47 line 3 from “...single-use surgical instruments if managed properly...” to “...single-use surgical instruments where appropriate if managed properly...”.
9. There were no matters arising.

ITEM 3 – CURRENT ISSUES

10. The Committee was updated on the following issues:
- A letter had been received from the UK Blood Services (UKBS) requesting SEAC advice on the use of commercial prion reduction filters for blood. The Chair suggested that it was not the role of the committee to validate commercial products or endorse their use. Members strongly recommended that the UKBS should

commission an independent validation of such products. However, once such a validation had been completed and a risk assessment conducted to examine the efficacy of the filters in reducing transfusion associated prion disease transmission, the committee could comment on the data presented. A letter to include these recommendations would be sent to the UKBS.

- Professor Medley informed members that the SEAC Epidemiology Subgroup would meet on 11 May 2005 to discuss the issues related to the future profile of the vCJD epidemic identified by SEAC at its last meeting.
- It was recently announced that the MRC Prion Unit and GlaxoSmithKline were collaborating to develop prion disease therapies.
- In France there has been a proposal to increase the testing of goats for BSE.
- The recent case of probable iatrogenic CJD related to a certain type of dura mater graft performed in 1987. The committee noted that the TSE related risks associated with this procedure were now well known and that such grafts no longer take place in the UK.
- A number of SEAC members had considered a submission from a member of the public hypothesising that toxic alkaloids in ryegrass may have been a contributing factor in the BSE epidemic. The members had agreed that the evidence put forward in support of this hypothesis was not sufficiently rigorous or compelling to warrant a full discussion. Furthermore, the evidence that contaminated meat and bone meal was the primary cause of BSE epidemic remains strong and the information provided did not persuade them to alter this view. The committee agreed that it would be appropriate for a letter to be sent to the member of the public along these lines. The committee stressed it welcomed submissions of evidence on alternative hypotheses for the causes or origins of BSE provided that there was sufficient supporting data to allow hypotheses to be discussed.

ITEM 4 – EARLY PHASE OF vCJD INFECTION IN RECIPIENTS OF BLOOD TRANSFUSIONS (SEAC 87/3)

11. The Chair informed members that the Committee on Microbiological Safety of Blood Tissues and Organs (MSBTO) had requested SEAC advice. MSBTO asked whether a scientific distinction could be drawn between tissue/organ donors that have

received blood transfusions either a few days or up to a week before donation (recent blood recipients), or in the more distant past (historic blood recipients), in terms of the relative load of vCJD agent that might be present in bone, tissues or organs. A number of individuals receive blood transfusions shortly before they die and become tissue/organ donors. Thus, the question related to whether there is a significant risk of vCJD transmission associated with such blood transfusions for the recipient of the tissues or organs. The advice from SEAC would inform possible risk reduction measures under consideration by the MSBTO. A SEAC statement would be drafted on the basis of the discussion.

12. Dr Marc Turner (UK Blood Services and Co-Chair of the Bone and Tissue Subcommittee of the MSBTO) provided the background to the MSBTO request. Since the identification of two cases of probable blood transfusion associated transmission of vCJD, the Blood Services, on the advice of the MSBTO, have deferred blood donors who themselves have received blood transfusions. This measure was instituted to reduce the possibility that blood transfusions could contribute to a self-sustaining vCJD epidemic.
13. Dr Turner explained that the potential risks of vCJD transmission associated with cell/tissue/organ transplants had also been considered by a vCJD Subcommittee of the MSBTO. Deferral of cell/tissue/organ donors that had received a blood transfusion had been considered. However, in the case of donors of bone marrow, kidney, liver, heart and lung there are shortages. As the primary use is for gravely ill individuals, deferral would not be beneficial to patients. Therefore, for patients urgently in need of potentially life-saving operations, deferral of donors of such tissues/organs would not be instituted.
14. Dr Turner explained that the balance between the potential vCJD transmission risks and patient benefits for transplants of other tissues/organs such as bone, tendons, ligaments, corneas, heart valves and skin was less clear. These tissues were mainly derived from cadaveric donors and submitted to tissue banks. The majority of these donors will have received blood transfusions around the time of death whilst a smaller number will have received historic blood transfusions. It may be possible to introduce deferral of historic recipients of transfusions without incurring tissue shortages. However, deferral of all donors that had received blood transfusions would incur shortages. MSBTO was seeking advice from SEAC on whether a scientific distinction could be made between recent and historic recipients of blood transfusions, in terms of potential risk of vCJD transmission from transplants. If so,

could a threshold of transmission risk, in terms of the time following transfusion for recent and historic transfusion recipients, be defined.

15. Members noted that there were very few data available to answer these questions. It was suggested that some distinction could be made between the current risk of transmission via a blood transfusion, and the historic risk prior to the introduction of precautionary measures such as leucodepletion and the restriction on recipients of blood transfusions from donating blood. It was noted that measures such as leucodepletion reduced, but did not eliminate infectivity in blood.
16. One member noted that two papers by Beringue *et al.*¹ that describe early accumulation of PrP^{res} in the spleen of mice following intraperitoneal inoculation with scrapie complemented the data presented in SEAC paper 87/3. In the studies, PrP^{res} was detectable in the spleen within one hour post-inoculation, increased to a peak at 4 hours, decreased at 6 hours and was undetectable from 12 or 24 hours before increasing again at between 5 and 7 days post-inoculation. Although the timing of PrP^{res} accumulation in these studies differed compared with the reports presented in SEAC paper 87/3, this was probably due to strain specific differences in incubation time. It was noted that most of the inoculum would accumulate, not in the spleen, but in the liver and lung following injection.
17. Members asked whether the increase in splenic PrP^{res} in the first few hours post-inoculation reported in the studies by Beringue *et al.* (2000) was due to accumulation of the inoculum or replication. Members were informed that the increase was thought to be due to accumulation of the inoculum. The inoculum was possibly then degraded before replication subsequently allowed the agent to be detected again almost a week later. Another member explained that although it was not possible at present to definitively distinguish between agent accumulation and replication, on-going work at the Institute of Animal Health lent support to this suggestion. Studies to differentiate between these two processes were underway. It was likely that the timing of these processes would differ between different strains of agent.

¹ Beringue *et al.* (2000) Pharmacological manipulation of early PrP^{res} accumulation in the spleen of scrapie-infected mice. *Arch. Virol. Suppl.* 39-56.
Beringue *et al.* (2000) Role of spleen macrophages in the clearance of scrapie agent early in pathogenesis. *J Path.* 190, 495-502.

18. One member noted that in most of the animal studies under consideration, brain homogenate had been used as the inoculum. The infectious agent in such preparations was likely to be in a more aggregated form than when endogenously produced in human blood. Accumulation of a more aggregated form of a prion agent by the liver, lung and spleen would be relatively more efficient.
19. In response to a question about the level of infectivity in the blood of rodent models, members were informed that no studies have examined the period immediately following inoculation. Infectivity was difficult to detect in rodent blood.
20. It was noted that the findings from animal models suggest that there may be windows of increased or decreased risk within the first week following transfusion. However, members considered that the data available were too limited, and could not be directly applied to define windows of lesser or greater transmission risk from human tissue/organ transplants.
21. It was suggested that, on the basis of the evidence available, the prion agent would have insufficient time to replicate in recipients of a recent, compared with a historic, blood transfusion. Thus, the transmission risk following transplantation of a tissue/organ from a historic transfusion recipient could be higher than from a recent transfusion recipient.
22. In view of the large proportion of the inoculum sequestered by the liver, lung and spleen, a member asked whether other tissues/organs could be relatively free of the inoculum. Members considered that in the early phase of prion infection following intravenous administration, the tissue infectivity levels would correlate with the blood supply to, and blood content of, tissues. In contrast to times much later in the incubation period, no distinction could be made between tissues of the lymphoid and central nervous system and other types of tissue in terms of infectivity levels. Thus, in the early period following a transfusion with infected blood, highly vascularised organs such as the liver, lung and spleen, as well as bone would be more likely to carry infectivity. Thus, a distinction could be made between tissues that are highly vascularised and those that are not, in terms of potential infectivity levels within the first week following blood transfusion.
23. In response to a question about the turnover of tissues in tissue banks, Dr Turner explained that it was dependent on tissue type. For example, turnover of heart valves was relatively small but

turnover of corneas was larger because they can only be stored for a short time. Members suggested that data on the turnover or lifetime of tissues in tissue banks could be used in conjunction with information on the timing of measures to protect the blood supply to make some assessment of the relative risks posed by the use of specific types of tissues/organs.

24. Members asked whether it was possible to screen tissue/organ donors for markers of infection. Dr Turner explained that in principal, it would be possible to analyse tonsillar and splenic samples from cadaveric donors for the presence of PrP^{Sc} before tissues were used. However, the time taken for tests precluded screening of donors before the use of some tissues with a short *ex vivo* lifetime such as organs and corneas. A feasibility study for the screening of cadaveric donors was under consideration. One member suggested that retrospective screening of donors would also help to inform assessment of transmission risks but noted that ethical considerations would influence such a strategy. Dr Turner indicated that such strategies were under consideration but the associated ethical issues raised difficulties.
25. Given tissue infectivity levels in the very early stage of infection are likely to be associated with blood, members asked whether it was possible to wash tissues to remove blood and therefore infectivity. Dr Turner explained that solid organs are perfused, but that even after perfusion organs are likely to contain significant quantities of residual blood. Tissues such as tendons and heart valves are stringently cleaned. The UK Blood Services are currently investigating processes to remove the blood and bone marrow from bone. The committee considered that it was important to investigate processes that would efficiently remove blood and bone marrow from bone but noted that some processes may damage the integrity of the bone itself. The committee noted that SEAC had advised previously to avoid pooling of tissues, such as bone, which reduces transmission risks by ensuring a one to one relationship between donor and recipient, preventing possible multiple transmissions.
26. Members questioned the large numbers of cadaveric donors that are transfused before death, asking whether all such transfusions were necessary. Dr Turner indicated that a review of the use of blood was underway, however blood transfusions were normally conducted to manage underlying medical conditions. In the past, some donors had been transfused with blood prior to donation to induce an immunologically suppressive effect, increasing the

success of transplantation. More sophisticated methods to suppress the immune system are now used.

27. Members considered that, because of a small background risk of vCJD infection in the population as a whole, tissues/organs from donors that had not received a blood transfusion carried some risk of vCJD transmission. It was noted that recipients of blood products from vCJD cases had been notified and deferred from tissue/organ donation. All recipients of tissues/organs were also deferred from blood transfusion. A member considered that it would be important to provide to potential tissue/organ recipients clear information on the risk of vCJD transmission via the transplant relative to the risks and benefits of undergoing surgery.
28. Members noted that, until sensitive ante mortem tests, especially for blood, became available it may not be possible to conduct definitive experiments that would further inform assessment of the transplant associated risks of vCJD transmission.
29. In summary, the committee concluded that:
 - current transmission risks associated with blood transfusion are lower compared with historic risks prior to the introduction of precautionary measures to reduce potential prion infectivity in blood.
 - on the basis of the very limited evidence available it is unlikely that significant replication of PrP will have occurred in the first week following a transfusion with infected blood.
 - tissue infectivity levels in the first week following transfusion with infected blood will be related to the blood supply to tissues. Thus, a distinction may be made between highly vascularised tissues and other tissues in terms of their potential infectivity levels within the first week following blood transfusion.
 - if possible, screening of cadaveric donors for the presence of abnormal PrP prior to transplantation, washing tissues/organs to remove blood before their use, and avoiding the pooling of tissues, may reduce transplant associated transmission risks. Limiting the numbers of unnecessary blood transfusions would also reduce risk.
 - a balance must be struck between the small increased risk of prion transmission by transplantation, and the benefits to patients receiving a transplant, especially where tissues/organs are scarce and are required for potentially life-saving procedures. It would be important to explain the risks and benefits to potential recipients of tissues/organs.

ITEM 5 – REPORT FROM THE AD HOC EPIDEMIOLOGY SUBGROUP ON UK BARB CASES

30. The Chair explained that in 2003, SEAC recommended that further investigations, such as a case control study, were important to aid understanding of BSE cases born after the 1996 reinforced feed ban (known as BARB cases). The SEAC *ad hoc* Epidemiology Subgroup on UK BARB cases was convened in March 2004 to advise on the design of a case control study and recommended a phased approach. Professor John Wilesmith presented the statistical analysis of the initial results of the study to the Subgroup in April 2005.
31. Professor Gill (Subgroup Chair) explained that the remit of the Subgroup was to advise on the design of the study and analysis of results and to recommend further work whether appropriate. The epidemiology of the 99 BARB cases identified up to 6th April 2005 in Great Britain, and the 13 cases identified in Northern Ireland, were described at the Subgroup meeting. It was unclear from these data whether the incidence of BARB cases was currently falling, or constant. The preliminary case control analysis presented included 93 BARB cases of which 67 cases were ascertained by active surveillance and 26 by passive surveillance. The Subgroup noted that the latest BARB case, born in October 2001, had been identified by active surveillance, highlighting the importance of active surveillance to ascertain BARB cases.
32. The controls used were derived from suspect cases subsequently tested negative for BSE (passive surveillance). Concerns had been expressed regarding possible selection biases arising from use of these passively ascertained controls for predominantly actively ascertained cases. Control selection was biased towards dairy-associated factors, feed histories, geographical location, previous BSE in the herd, and contact with other animals on farm. These were all critical factors to the study. The Subgroup considered that passively ascertained controls were appropriate for BARBS ascertained through passive surveillance. The Subgroup had made a number of recommendations for further statistical analysis of the results.
33. The Subgroup highlighted the importance of understanding the feed history of BARB cases, since feeding practices had changed over the last 10 to 15 years. In anticipation of BARB cases arising in the future and the need to trace their feed history, the Subgroup recommended that a study should be undertaken of present

feeding practices and potential for cross-contamination. Dr Danny Matthews (VLA) agreed such a study should be carried out but commented that if BARBs were caused by the cross-contamination of feed with low doses of TSE infectivity then such a study may not be able to detect that it was occurring. Only ingredients acknowledged to be incorporated would be identifiable. The committee agreed a study of feeding practices was important and noted that, although it was unlikely that conclusive evidence would be obtained for particular feed practices being associated with BARB cases, such a study may give insight into possible controls that might be applied if BARB cases continue.

34. A member pointed out that at a recent meeting, Zanusso *et al* had presented profiles of sporadic CJD cases analysed by a 2-D Western blot technique to produce detailed protein fingerprints to distinguish PrP profiles. It was suggested that this technique could be used to characterise the PrP profile of BARB cases. The committee agreed that this approach could provide valuable information.
35. Dr Matthews indicated that the VLA would review the status of BARB case samples to see if this analysis was possible. However, many samples had been used for DNA sequencing and other analyses. Furthermore, because the majority of BARB cases had been detected through active surveillance, many samples were autolysed, which may preclude meaningful interpretation of 2-D Western Blot analysis. He noted that when samples from BARB cases had been analysed using conventional western blot analysis, the samples had shown profiles consistent with historical BSE. The DNA sequence data of BARB cases would be available in June, though no significant differences in sequences of cases and controls had yet been found.
36. In conclusion, SEAC agreed that it was too early to interpret the data from the preliminary case study and concurred with the *ad hoc* Epidemiology subgroup on UK BARB cases recommendations, which were to:
 - perform further work to include herd type in the multivariable analysis,
 - repeat the analysis on the 26 passively ascertained clinical BARB cases, acknowledging the effect on the study power,
 - repeat the preliminary analysis to include ten controls selected from the Cattle Tracing System to match each BARB clinical case ascertained by passive surveillance in respect of date of birth and age of clinical BSE diagnosis.

- perform an analysis using a biostatistical approach to study space/time clustering of all BARB cases,
 - perform prospectively an evaluation of animal feed use and supply routes and the potential for cross-contamination of feeds.
37. In addition, SEAC agreed it was important to pursue these recommendations urgently together with new, more sophisticated molecular approaches for characterisation of BARB cases. It was also important to gather as much information as possible on cases as they arise.

ITEM 6 – AOB

38. An updated and amended Code of Practice for SEAC members was tabled, whereby items in reserved session are subject to strict criteria, such as information related to patient confidentiality and prepublication data. It now reflects requirements under the Freedom of Information Act (FOI). The Code also refers to discussions during the period of 'purdah' preceding a general election.
39. The Chair asked members to send any comments on the amendments to the secretariat as soon as possible.
40. The Chair asked members to respond to the secretariat's trawl for 2006 meeting dates as soon as possible.

AFTERNOON SESSION

ITEM 1 – CHAIR'S INTRODUCTION

41. The Chair explained that the Committee had planned to discuss all of today's agenda items in open session. However, due to the period of 'purdah' preceding the General Election, two items would be discussed in a closed afternoon session. The papers would be placed on the website as soon as possible after the general election.

ITEM 2 – VERTEBRAL COLUMN: AGE AT WHICH SPECIFIED RISK MATERIAL (SEAC 87/2)

42. The Chair explained that the committee had been asked by the FSA to comment on the scientific validity of the approaches used, and the assumptions made, in a risk assessment on under 30 months beef on the bone, and to comment on the findings.

43. Mr Alan Harvey (FSA) provided the background to the issue. In 1997, the Ministry of Agriculture, Fisheries and Food had imposed a ban on beef on the bone in the UK on the basis of SEAC advice that there was a small risk that prion infectivity could be transmitted to humans through consumption of residual dorsal root ganglia (DRG) associated with the vertebral column. In 2000, the ban had been lifted for discrete cuts of meat from under thirty month cattle, where bone was obviously present, but not for processed meat products. Thus, consumers could choose to eat beef on the bone.
44. Under present EU TSE regulations, the vertebral column of cattle over 12 months is classified as specified risk material (SRM). Currently the UK has a derogation whereby vertebral column is classified as SRM for cattle aged over 30 months. This UK derogation was authorised due to the UK demonstrating the effectiveness of restrictions placed on animal feed, and on the basis that UK beef is not exported. Recently the European Food Safety Authority (EFSA) has indicated that the UK BSE status may be re-categorised from “high risk” to “moderate risk”. This would allow beef exports to resume, but only if the UK adopted the same TSE rules as other EU member states. EFSA would be conducting a risk assessment on harmonising rules on the SRM age limit for vertebral column. In view of this, the FSA have commissioned DNV Consulting to assess risk from under thirty-month beef on the bone¹, which would be presented to EFSA.
45. Mr Philip Comer (DNV Consulting) provided an overview of the risk assessment. The change in risk to the UK population from reducing the age limit for vertebral column as SRM from 30 to 12 months of age had been analysed. The risk assessment was built on previous assessments undertaken for the FSA, as part of the review of the over thirty months rule (OTM)². In addition, current data on BSE infectivity had been reviewed, updated, and combined with data on butchery practices and their impact on the removal of DRG. The infectivity of tissues was calculated taking account of the new data from the VLA’s second stage cattle attack rate experiments, and the Scientific Steering Committee (SSC) report (2000). The number of infected animals slaughtered for food was derived from the OTM review studies by Ferguson and Donnelly (2003)⁵.

¹ DNV Consulting (2005). Assessment of Risk from Under Thirty Month Beef-on-the Bone: Report for the Food Standards Agency.

² Comer PJ and Huntly PJ (2004) *Journal of Risk Research* 7, 523-43

⁵ Ferguson NM and Donnelly (2003) Pro R Soc London, Biological Sciences: The Royal Society.

46. Mr Comer explained that it was estimated that five million bovine oral ID₅₀ units entered the UK human food chain from 1980 to 2001. Thus, the average exposure over this time would have been 0.004 bovine oral ID₅₀ units per person per year. Although the exact size of the cattle-human species barrier was unknown. Clarke and Ghani (2004)³ had estimated 70 future vCJD deaths with an upper limit of 400. Using the upper estimate, the species barrier for methionine homozygous individuals could be estimated to be of the order of 4000. However, the species barrier would be of the order of 400 if it was calculated on the basis of the number of infections (3800) estimated by Clarke and Ghani (2004).
47. Mr Comer explained that two types of butchery practices were used in the UK to bone meat, sheet boning and traditional boning. Studies had suggested more DRG was found in meat butchered by the traditional method. Assumptions had been made in the assessment about the proportion of the two methods used in butchery practice.
48. Mr Comer concluded that the present UK BSE exposure would be a median value of 0.07 bovine oral ID₅₀ units per year with vertebral column included for under thirty month animals. This was an extremely low exposure considering that it was the total exposure for the whole UK population over one year. Furthermore, this level of infectivity did not take into account the large species barrier. If the vertebral column of animals were to be classified as SRM from 12 months of age the median exposure would reduce from 0.07 to 0.05 bovine oral ID₅₀ units per year. The proportion of DRG consumed would reduce from 2.2 to 1.65%. In a hypothetical worse case scenario, if one fully infected animal entered the food supply, exposure would be 3 bovine oral ID₅₀/year, reducing to 2.4 bovine oral ID₅₀/year if vertebral column was SRM.
49. A member asked whether the estimated level of infectivity going into the food chain was calculated using a single value or a distribution of infectivity. It was explained that a distribution of infectivity had been included but that this was related to a single infected animal entering the food chain 11 months before clinical disease. The risk assessment was sensitive to the infectivity values used. A member queried whether potential failure of SRM controls had been taken into account in the assessment. It was explained that as part of the OTM rule review study, the spread of infectivity by maceration of spinal cord during butchery was

³ Clarke P and Ghani AC (2004) *J R Soc Interface*

considered but even with this additional infectivity, exposures were still relatively low. Members noted that pessimistic assumptions had been made on infectivity levels based on data available from attack rate studies.

50. Members noted that the assessment had not specifically considered whether there might be a small cohort of beef on bone consumers. Estimations of the likely maximum infective dose to individual people and of the exposure to beef on bone consumers would be useful. Mr Comer explained that there were no data available for this population subgroup.
51. Members considered that there were uncertainties about the size of the cattle to human species barrier, and noted that recent published data on experimental oral transmission of BSE to primates had suggested a species barrier of 7 - 20.
52. In summary, the committee concluded that it was content with the approach used and assumptions made in the risk assessment. It noted that:
 - the assessment included a pessimistic assumption about the levels of infectivity entering the food chain from residual DRG associated with vertebral column
 - some uncertainties remained with regard to the extent of the species barrier between cattle and humans.
 - the risks were calculated for the UK population in general and not specifically considered the UK beef on the bone consuming population. However, although exposure would be higher in this group than assumed in the assessment, the risk to this population group is still likely to be very small.
 - the change in classification of vertebral column as SRM from 30 months to 12 months would make a very small to negligible difference in risk, even to the small number of people who consume beef on the bone.
53. The Chair explained that the FSA required a short statement on the committee's discussion to present to EFSA the following week. In view of the short time available to prepare the statement, the committee agreed that the statement would be cleared by Chair's action.

ITEM 3 – USE OF CATEGORY 3 ANIMAL BY-PRODUCTS IN FERTILISER (SEAC 87/4)

54. Mr Steve Wyllie (Defra) provided the background to the issue. In 1996 the use of MMBM in fertiliser for agricultural land was banned to cut off potential routes of TSE exposure to livestock. In 2002, EU legislation was introduced that classified animal by-products (ABP) into Category 1 (high risk material from animals with suspected or confirmed TSE), Category 2 (condemned meat from diseased animals) and Category 3 material (fit for human consumption). Category 2 and 3 material was permitted to be used as fertiliser, but in the case of all Category 2 material, and Category 3 material of mammalian origin, only if reduced to a particle size <50 mm and pressure cooked (>133°C and 3 bar for 20 minutes). In addition, category 3 material could be used in compost if reduced to <12 mm and heated to 70°C for at least one hour. Appropriately-treated Category 2 and 3 ABP could be applied to non-pasture land. Non-pasture land included a period when farmed animals cannot graze. A three week non-grazing period is currently being proposed by the Commission, based on an EFSA opinion.
55. Mr Wyllie explained that, in contrast to the EU regulations, no rendered MMBM is allowed in fertiliser spread on any agricultural land under current UK regulations. An anomaly also exists within UK legislation as category 3 ABP can be treated in a biogas or composting plant and applied to land. However, if it is treated in a rendering plant it is designated as MMBM and cannot be applied to agricultural land even though it is treated under more severe conditions than it would in a composting/biogas plant. Defra is considering amending the UK legislation to address the anomalies and align UK with EU regulations. As an initial step, Defra commissioned VLA to conduct a release assessment (RA) to estimate the TSE-related risks associated with the use of rendered Category 3 ABP as fertiliser on non-pastureland.
56. Dr Amie Adkin (VLA) presented the methods, inputs and assumptions made in the RA together with the results. The RA considered scenarios of scrapie in sheep, theoretical BSE in sheep, and BSE in cattle, under current conditions, and assessed the impact of removal of the OTM Rule. The RA consisted of four successive modules:

Farm Module

57. The farm module estimated the numbers of cattle and sheep within the last 12 months of incubation of scrapie or BSE, that are slaughtered for human consumption per year. It was assumed that BSE is present in the national sheep flock and the prevalence of

BSE or scrapie is not stratified by age, a lamb having the same probability of being infected in the national flock as an adult sheep.

Slaughter Module

58. Using data from the farm module, the slaughter module estimated the quantity of infectious material (expressed as oral ID₅₀), passed as fit for human consumption, leaving slaughterhouses per year. For BSE in cattle it was assumed there was no risk associated with liver, kidney, lung, stomach, blood and trimmings. It was also assumed that animals are fully infected and that carcass contamination of the food chain could occur via four routes: insufficient removal of spinal cord, spinal cord contamination from splitting the carcass, brain tissue from the captive bolt used in slaughter, and the presence of DRG.
59. For the scrapie and BSE in sheep models it was assumed that positive animals were fully infected, the infectivity for BSE in sheep is the same as scrapie, and that carcass contamination of the food chain could occur via two routes: insufficient removal of spinal cord and via infectious tissues not designated as SRM.

Rendering module

60. Using the information from the slaughter module, the rendering module estimated the concentration of infectivity in fertiliser (oral ID₅₀ per kg). It was assumed that all TSE infectivity remaining on the carcass after SRM controls subsequently enters category 3 waste. This was a pessimistic assumption as other routes such as landfill, composting or ingestion which would reduce infectivity levels were not included. It was assumed that 50-75% of Category 3 MMBM would be used in fertiliser production.

Land module

61. The land module estimated the infectivity of TSE on non-pasture land three weeks post application (oral ID₅₀ per m³) on the basis of the estimates from the rendering module. It was assumed there was no decay of TSE in soil, no leaching of TSE beyond 1 cm of topsoil, and that the yearly input of fertiliser to land is applied in one dose.
62. Dr Adkin explained that the final results of the study related to infectivity in soil available per year, not the probability that a cow becomes infected. The exposure of cattle to that infectivity was outside the scope of the RA. Information on the frequency of cattle

on non-pasture land, the length of stay and consumption of soil and vegetation would be required for an exposure assessment. The final results from the land module were (with 5th and 95 percentiles):

- The average TSE infectivity on non-pasture land per year from cattle with BSE would be 2.0×10^{-11} bovine oral ID₅₀ per m³ (1.7×10^{-12} , 6.1×10^{-11})
- The average TSE infectivity on non-pasture land per year from sheep with BSE would be 5.0×10^{-9} ovine oral ID₅₀ per m³ (1.3×10^{-10} , 1.8×10^{-8})
- The average TSE infectivity on non-pasture land per year from sheep with scrapie would be 2.4×10^{-6} ovine oral ID₅₀ per m³ (3.9×10^{-7} , 5.8×10^{-6}), 500-fold greater than for BSE in sheep.

63. Dr Adkin indicated that the model was sensitive to the amount of MMBM fertiliser applied annually, the effect of rendering on TSE infectivity, the titre of TSE infectivity in tissues and, in the scrapie model, the proportion of natural scrapie that is BSE. Removal of the Over Thirty Month Scheme (OTMS) would increase BSE infectivity 60-fold but infectivity levels would still be extremely low. A worst case scenario had been modelled assuming a fully infected entire BSE carcass including SRM was rendered into one batch of fertiliser (a one in a million million occurrence). In this case, the BSE infectivity on non-pasture land would increase by 6 orders of magnitude from a mean estimate of 2.0×10^{-11} bovine oral ID₅₀ per m³ to a mean of 5.0×10^{-5} bovine oral ID₅₀ per m³.
64. In opening the discussion, the Chair indicated that the RA had been sent to an independent epidemiologist Professor Dirk Pfeiffer (Royal Veterinary College, London) for review. Professor Pfeiffer concluded the RA was logically structured and the data and assumptions clearly described. The results had been presented with due consideration of the assumptions. He noted that the processes used in developing the model, obtaining the data and scrutinising the model were not documented. It was unclear whether the quality of unpublished and published data was scrutinised or taken at face value. In summary, the model structure was appropriate and the conclusions plausible. Improved documentation would enhance the credibility and transparency of the model outputs.
65. A member had also reviewed the RA in detail and concurred that the RA was thoroughly carried out. It was noted that, with the OTMS, the RA had assumed an infectivity level leaving the slaughterhouse of 140 bovine oral ID₅₀ per year whereas other risk

assessments had used lower values. Dr Adkin commented that the difference was due to inclusion of a fully infected carcass, rather than considering carcasses at different points in the incubation period. In addition, the model contained different routes of contamination of the carcass post SRM controls that are not included in other assessments. It was suggested that the assumption of all infectivity remaining on a carcass entering category 3 waste and being spread as fertiliser was perhaps overly pessimistic.

66. Dr Adkin was asked why no uncertainty estimate had been included regarding the OTMS removal scenario. Dr Adkin indicated that the estimates for the number of infected cattle to slaughter were based on a peer-reviewed back-calculation model from Arnold and Wilesmith (2003)². The model had not been set up to provide the 5th and 95th percentiles in the case of OTMS removal. This had now been explored and the overall results had not changed significantly as a result of including the uncertainty estimate. Dr Matthews added that a previous qualitative risk assessment indicated the risk was very low, and he felt the correct approach for a quantitative RA was to use pessimistic assumptions. There were many uncertainties in terms of the process once material left the abattoir, regarding rendering plant used, volumes of waste and how this material would be used subsequently, therefore estimates had been based on consultation with industry representatives, and if estimated infectivity levels remained low even with pessimistic assumptions this could be considered reassuring.
67. A member noted that the assumptions in the RA were dependent on effective enforcement. It was suggested that a 3 week non-grazing period could be difficult to enforce. In addition, it had been assumed that no imported MMBM was used in fertiliser. Enforcement should be considered in developing policy.
68. It was noted that even distribution of infectivity in fertiliser, and its even distribution across land had been assumed. In reality, TSE infectivity spread would be heterogeneous. Dr Adkin explained that this scenario had been addressed to some extent by the worst case scenario in which a fully infected entire BSE carcass was rendered into one batch of fertiliser.
69. Dr Adkin added that it had been assumed that there was no degradation of prion protein during the assumed 3 week non-

² Arnold M. and Wilesmith J.W. (2003) Modelling studies on BSE occurrence to assist in the review of the over thirty months rule in Great Britain. *Proc Roy Soc Lond B* 270, 2141-2145

grazing period. Members considered that should TSE agents persist in soil, infectivity could accumulate over time. Dr Adkin indicated that the accumulation of infectivity over time was not addressed, as an exposure assessment had not been carried out. In order for such accumulation to occur TSE infectivity would have to be applied on multiple occasions to the same location, which may be unlikely. One study indicated there would be 98% decay of the agent over 3 years³. Dr Matthews observed that accumulation would be against a backdrop of decreasing TSE prevalence. Mr Wyllie added that Defra- and EU-funded research is being conducted to investigate the behaviour and degradation of TSE agents in soil.

70. A member considered that, since the TSE agent is a protein, it was likely to decay quickly due to the pH of, and bacteria present in, soil. However, a member pointed out good evidence suggesting that the Chronic Wasting Disease agent persisted in the environment. Dr Matthews informed members that a VLA project on infectivity in sheep exposed to the farm environment indicated that material on pasture is infectious for at least 2 months. Members agreed that in view of the resistance of PrP^{Sc} to degradation, evidence from CWD and the VLA studies, it was safer to assume survival of the agent in soil for a significant amount of time.
71. In response to members' questions about the field spreading of fertiliser, Alan Brewer (Defra) informed the committee that some dust can arise from the activity, both from the fertiliser distribution process (that depends on the type of spreading mechanism) and from tractor wheels kicking up soil in arable situations. But it was not possible to indicate whether there was any likelihood of dust particles containing fertiliser drifting onto adjoining fields. He added that it was recognised as good practice for farmers not to spread fertiliser into hedges and watercourses.
72. Members asked whether cross-contamination between category 2 and category 3 material could occur on processing. Mr Wyllie indicated that Category 2 and Category 3 materials had to be rendered in separate buildings, although these could be on the same site.
73. Members asked if the final result of the RA could be an overestimate of scrapie infectivity due to the assumption that all sheep were adults. Dr Adkin indicated this may be a pessimistic

³ Brown P. and Gajdusek D.C. (1991) Survival of scrapie virus after 3 years' interment. *Lancet* 337, 269-270

assumption as adult sheep have larger tissue sizes. Dr Matthews commented that genotyping studies from the abattoir survey indicated there is a high prevalence of arginine-carrying sheep at codon 171 and that therefore infectivity was more likely to be restricted to the central nervous system rather than other tissues and the RA had assumed the worst case.

74. Members noted that infectivity in fertiliser has the potential for intraspecies recycling and poses a different risk from dead-end infections. It was recommended that surveillance was essential to detect infected animals and identify such a cycle.
75. It was noted that multiple risk assessments tended to consider single routes but often routes were cross-linked. It was suggested that consideration should be given to risk assessments that consider such links rather than specific routes in isolation. Members asked whether risk assessments could be produced in a consistent way and asked if there was a forum to discuss inputs to risk assessments. Dr Matthews indicated that a “Neuroprion Risk Assessment” group was looking to peer review data and generate a consensus for risk assessments. Dr Adkin indicated within the EU, risk analysts are reviewing parameters to enable comparison of models.
76. In summary, the committee concluded:
- it was content with the approach used and assumptions made in the risk assessment.
 - the assessment predicted that TSE infectivity levels on land as a result of the application of fertiliser would be extremely low. However, because of the likely heterogeneous nature of infectivity in fertiliser and the uneven spread of fertiliser, TSE infectivity levels might be higher in some geographical locations than predicted.
 - controls to ensure that category 3 material is processed separately from Category 1 and Category 2 material be audited.
 - a watching brief be kept on CWD and BARB cases to assess the possible persistence of the agent in the environment.

ITEM 4 – AOB

77. The Chair thanked VLA for SEAC paper 87/7 which provided an update of current VLA research on TSEs.

78. A member suggested that it might be timely to consider review of the National Scrapie Plan (NSP) either by SEAC or by the Sheep Subgroup. The purpose of the NSP was to reduce the incidence of scrapie in the national flock and to protect consumers against the theoretical risk of BSE in sheep. When the NSP had been put in place it had been agreed that it would take into account new data as it emerged. It was agreed that the secretariat would contact relevant groups to see if there were new data which would justify a review by the sheep subgroup in the near future.

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