

FINAL



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Minutes of reserved business of the 80th meeting held on 26th November 2003

At

Church House Conference Centre
Dean's Yard
Westminster
London

Members: Professor P. Smith (Chairman)
Professor A. Aguzzi
Professor R. Anderson
Professor C. Bostock
Professor G. Bulfield
Professor R. Carrell
Mr P. Jinman
Professor H. Kimbell
Professor C. Masters
Professor I. McConnell

Technical Advisors: Dr P. Barrowman (Defra)
Dr S. Dixon (FSA)
Mr P. Soul (Defra)
Dr J. Stephenson (DH)
Dr D. Matthews (VLA)

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

SEAC Secretary: Dr C. Boyle

Observers: Dr Y. Boyd (Defra)
Dr G. Cadwallader (MRC)
Dr P. Christie (SE)
Dr P. Crook (EA)
Dr A. Douglas (DARDNI)
Dr I. Hill (FSA)
Dr M. Simmons (NAWAD)
Dr H. Tyson (BBSRC)

Secretariat: Mr M. Pemberton
Dr B. Jeffery
Dr P. Keep
Dr C. Ravirajan
Ms T. Dale

Also in attendance: Dr P Bennett (Paper 80/6)
Professor T Chambers (Paper 80/6)
Dr J Tinckler (Paper INF/80/8)
Professor D Jeffries (Paper INF/80/9)

Item 1 – Chair’s Introduction

1. The Chair welcomed Dr Peter Bennett (Department of Health), Professor Tim Chambers (St George’s Medical School), Dr. Danny Matthews (VLA), Dr Jeremy Tinckler (Medical and Healthcare products Regulatory Agency, MHRA), and Professor Don Jeffries, the Chairman of the ACDP/SEAC TSE Joint Working Group (JWG), who were in attendance to present agenda items.
2. The Chair received apologies for absence from Professor James Ironside, Dr Jiri Safar and Dr Corinne Lasmezas. The Chair informed the committee that Professor Adriano Aguzzi had to leave the meeting at 3:30 pm.
3. Under the SEAC code of practice, certain issues may be considered in a reserved business session of the committee. Where the information required to provide advice was commercially confidential, pre-publication research data or subject to ministerial approval, such agenda items are considered in closed session unless the author gives permission for the information to be released in the public domain. With respect to the agenda of this meeting, most of the items included in the closed session fell under the category of awaiting ministerial approval for publication. Item INF/80/7, which provided an update of the ongoing cattle studies at the VLA contains unpublished data.

Item 2 - Approval of draft minutes from 24th June 2003 (SEAC 78) SEAC reserved business meeting (SEAC 80/5)

4. The minutes of 24 June meeting were agreed subject to one amendment:
 - change paragraph 39 line 2 from “Although the challenged animals were ARQ/ARQ, which in this flock do not succumb to natural scrapie, it cannot be guaranteed that they were from a scrapie free environment” to read “The challenged animals were ARQ/ARQ, which do not succumb to the natural scrapie that is present in this flock. Thus they were not sourced from a scrapie-free environment and cannot be guaranteed to be free of scrapie infection”.

Item 3 - vCJD infection risks associated with bone products for revision hip replacement (SEAC paper 80/6)

5. Dr Peter Bennett from the Department of Health introduced this item. The Chair introduced Professor Timothy Chambers, Head of Cellular Pathology at St George's Medical School, who had been invited to provide expert advice on bone biology. Professor Adriano Aguzzi declared a possible conflict of interest in his consultancy role for Geistlich, a company that produces medical devices suitable for use in re-constructive surgery.
6. The Department of Health's Economics and Operational Research (EOR) division, together with the National Blood Service (NBS) had produced a draft risk assessment on the risk of transmission of vCJD from implantation of bone. This followed previous work by EOR on the risks of transmitting vCJD via

donated blood, hospital surgery and 'high-street' dentistry, all of which have been endorsed by SEAC.

7. Clinically, the main use of bone is in revision hip surgery, where an existing artificial hip has to be replaced. Human bone is sourced by the NBS (or other bone banks) as single femoral heads (from living patients undergoing primary hip replacement) or from cadaveric donors. Alternatively, individual femoral heads may be taken and used locally.
8. Dr Bennett informed the committee that the risk assessment compared the risks associated with different bone products i.e. processed or unprocessed, pooled or unpooled, under different scenarios for vCJD infectivity and prevalence of infection in the population.
9. Patients receiving unprocessed bone products would also receive significant amounts of blood and marrow and this blood was not leucodepleted. Although there is no conclusive evidence that blood and bone marrow is infectious in humans, the draft risk assessment used the precautionary assumption that infectivity may be present. A linear dose-response model, similar to that used for blood infectivity, had been used, in which a dose of 2 ID₅₀s or above was taken as sufficient to cause certain (or at least highly-probable) infection. Data by Lomas *et al* (2000)¹ suggest that 98% of blood and marrow can be removed following washing and centrifugation steps. It was assumed that morcellisation of the bone (as in the NBS "processed" products) would allow more effective removal of blood and marrow, an NBS estimate of 99% removal being used as a baseline.
10. The risk assessment showed that the risk of transmission of vCJD from bone is affected by pooling and is dependent on the assumed level of infectivity. Processing of bone reduces the amount of blood and marrow, therefore the risk of infection from that source would be lowered. However if living (rather than cadaveric) donors are used, processing requires the pooling of several – typically 17 - donations. This is due to the relatively small mass of each individual femoral head. Pooling donations may constitute a greater risk because of the possibility of sourcing infectious material from any one of multiple donors. The EOR paper addressed the balance of risk between processing and pooling in different scenarios.
11. Dr Bennett described the possible scenarios involving the processing and pooling of bone.
 - If infectious doses transmitted remain below 2 ID₅₀s, then pooling does not change the expected number of infections for a given donor prevalence. Pooling of donations would result in a greater number of recipients receiving a small dose. Under a linear dose-response relationship, these considerations would cancel out. If infectivity were confined to blood and marrow, the key consideration would be the effective removal of this by

¹ Lomas R, Drummond O, Kearney JN. Processing of whole femoral head allografts: A method for improving clinical efficacy and safety. *Cell and Tissue Banking* 1:193-200,2000.

processing. In these scenarios, the risks associated with unprocessed femoral heads would be greater than for any of the other products.

- However in scenarios where doses exceed 2 ID₅₀s, the risk of infection is mainly determined by the number of donors in the pool. In high-infectivity scenarios, the disadvantages of pooling would outweigh the benefits of processing. This could occur if the mix of blood and marrow had high potential infectivity and/or if infectivity could reside in the bone itself.
12. The Committee's view was sought as to which of these scenarios appeared most plausible. Members queried if alternatives to human bone were an option for revisionary hip replacements. Professor Chambers informed the committee that he was unaware of alternatives that were in use or could be used for this procedure. Members were concerned that the equipment used to crush bone could become contaminated if inadequately cleaned which could result in carry over of infectivity from one batch to the next. The committee advised that if possible, the risk assessment should consider this possibility.
 13. The committee advised that in the absence of any experimental data on the distribution of infectivity of vCJD, it remains plausible that bone itself may carry infectivity as osteoblasts (bone forming cells) are of the same cell lineage as macrophages, which have been shown to exhibit PrP^{sc}. The committee also noted that if infectivity were demonstrated in bone, this could outweigh any risk from blood and marrow residues given the substantial volume of bone used. The committee commented that a review of the epidemiology of CJD had found limited evidence for bone allo- or xeno-grafts (sheep) transmitting CJD, however these results were not statistically significant.
 14. Members recommended that more research was required to investigate if bone cells could carry infectivity and the infectivity of bone from vCJD cases. The committee noted that in the 2003 WHO guidelines on TSEs (INFO 80/80) the infectivity of human bone had not been included and this remained an issue of uncertainty.
 15. The committee was informed that transmission studies using bovine bone collected 18 and 32 months post-challenge from cattle challenged orally with BSE were negative for infectivity in assays involving intracerebral and intraperitoneal inoculation of RIII mice. The CNS was infectious in the donor animals at 32 months post inoculation. However, it was noted that given the reduced peripheral pathogenesis in BSE-infected cattle, the research on bovine bone may not be a useful indicator for the vCJD agent in human tissues.
 16. On the relative infectivity of blood and marrow, Professor Chambers commented that the cellular density of marrow was significantly greater (approximately 100-fold per ml) than blood, and this could increase infectivity. Blood was considered a good analogy for bone marrow given that 20-30% of bone marrow were B-cells. One approach to assess the relative risks would be to estimate the number of marrow cells provided in a bone graft and compare that with those used in a blood transfusion. However without clinical or experimental data

on the number of cell types within a bone graft it was difficult to complete this comparison.

17. The lipophilicity of the prion protein suggested that it could theoretically bind to surfaces such as bone. No data were available on the fat content of bone and the committee was not aware of any studies that measured the levels of PrP in bone or fat and thus could not discount the possibility that both could carry infectivity.
18. Members said it was not known what component of blood was infective. The committee noted the experimental data which showed that sheep bone marrow was not highly infectious, but marrow from scrapie-infected sheep had nevertheless been shown to infect other sheep.
19. The committee recommended that the transmission studies using bone marrow and blood should be reviewed in order to assess their comparative infectivity, respective cell density and volume transfused.
20. Professor Chambers commented that morcellisation would increase the surface area of the calciferous bone and aid removal of blood, fat or marrow by washing. Removal should therefore be more complete than with the centrifugation methods described by Lomas *et al.* Members agreed that Lomas *et al.* (2003) presented a relative measure of the efficacy of processing and that the 98% removal of marrow quoted in the paper had not been calculated from knowing the absolute amount of material present before processing.
21. EOR calculations assumed that infectivity would be unaffected by γ -radiation used in processing. Members were asked to comment on recent US research suggesting treatment with γ -radiation (50 kGy) lowered prion infectivity by an estimated 1.5 log₁₀ (Miekka *et al.* 2003²). In clinical settings, it was thought that 40 kGy was used on bone grafts. Members advised that this may not be sufficient to decrease the titre of infectivity materially and that γ -radiation was not a risk reduction option for bone donations. The risk assessment should continue to use “no effect” as a baseline assumption, but consider a possible infectivity reduction from γ -radiation in sensitivity analysis.
22. Members commented that the risk of transmission of vCJD from bone or blood and blood products was a theoretical possibility that had not been definitively demonstrated by experimental studies. The committee noted that the magnitude of risk of transmission of CJD from bone grafting was no easier to assess than the risk from blood transfusion, given the scientific uncertainties relating to where in blood infectivity resided and on the number of donors who are incubating vCJD. Further data from infectivity assays and transmission studies were required to inform on the risks from human blood and bone.

² Miekka SI, Forng RY, Rohwer RG, MacAuley C, Stafford RE, Flack SL, MacPhee M, Kent RS, Drohan WN. Inactivation of viral and prion pathogens by gamma-irradiation under conditions that maintain the integrity of human albumin. *Vox Sang.* 2003 Jan; 84(1): 36-44.

However the committee acknowledged the need for working assumptions to be made while these were ongoing.

23. Given that the uncertainties around infectivity were unlikely to be resolved soon, the committee endorsed the need for robust conclusions covering a wide range of scenarios. Other than reducing the use of bone, the most robust way of limiting any vCJD risk would be to use processed but unpooled bone where possible. Members were informed that the same risk reduction considerations should apply to any risk from sporadic, as well as variant CJD.
24. The remote risks from CJD from hip replacement must be put into context with the age and benefit for these patients. Members were reminded that bone products were nevertheless used in otherwise healthy patients who could live for a substantial length of time which may allow the development of clinical disease if transmission of CJD occurred.
25. Members were informed that the Department of Health planned a wider consultation of suppliers and users of bone (orthopaedic surgeons), to obtain views on the clinical preferences for bone products on grounds unrelated to vCJD (e.g. mechanical properties). The impact of any vCJD risk reduction measures on the bone supply to the NHS would also need to be taken into account, as the total supply had to meet the clinical need for bone.

Item – 4 Update on Defra funded research on cattle oral dose attack rate study (SEAC/INF/80/07)

26. Members were updated with details of the BSE oral attack rate and pathogenesis studies, which are funded by Defra and conducted by the VLA.
27. As at October 2003, six animals had succumbed to BSE after oral challenges ranging from 0.01-1.0 g bovine infected brain material. A single animal challenged with 0.001 g bovine infected brain material has also shown clinical signs typical of BSE. The animal would be slaughtered for further investigation and confirmation of transmission.
28. Members noted that in the previous study which used higher doses, a positive correlation between the incubation period and the oral dose was reported. No such correlation was so far observed in the lower dose range experiment. Members suggested that genetic polymorphism of the *Prnp* between cattle could explain the differences in dose response. It was thought that the cattle had the same *Prnp* polymorphism but this information would be clarified for the committee.

Update on bovine pathogenesis study

29. Members were informed that the VLA had no new data to present since the last SEAC meeting in June 2003.

30. The committee's recommendation to examine for the presence of PrP^{Sc} in tongue was proving difficult to conduct in practice, due to the limited availability and nature of the tissue from the original pathogenesis study.
31. Staff from the VLA and FSA were to discuss the future of the current bovine pathogenesis studies as animals could not be maintained in the study indefinitely and review points allowed termination of cattle if appropriate.

TSEs in sheep strain typing programme

32. Members were informed that the Community Reference Laboratory (CRL) expert group on strain typing met in October to review the progress of the ring trial in place to evaluate tests aimed at discriminating between experimental BSE and scrapie in sheep. The expert group had agreed that samples should be collected from the brain stem and macerated before testing. Unblinded bovine positive controls were to be submitted prior to testing, as some assays were species dependent. In January 2004, the next round of the ring trial is due to test ovine samples from animals with experimental BSE or natural scrapie.
33. The Committee noted that as the IAH derived scrapie strain CH1641 was not yet available in sufficient quantity, this tissue would not be included as a control in the survey. However the VLA modified western blot method had previously been shown to be capable of discriminating between CH1641 and ovine BSE, as had differential staining by immunohistochemistry.
34. The committee noted that the VLA had retrospectively tested 1280 (as at 21 November 2003), brain samples from scrapie positive sheep, of which 1237 were positive by western blot. The remaining 43 animals were to be re-tested due to weak or negative signals in the first test. Prospectively (between 1 November 2001 and 21st November 2003), 955 (n=1390) animals had tested TSE positive. None of the TSE positive sheep brain samples showed characteristics indicative of BSE.

Item 5 - The risks associated with medical devices containing ovine and caprine materials (SEAC paper INF/80/8)

35. Mr Jeremy Tinckler (MHRA) and Dr Rowena Jecock (DH) presented this item. The committee was asked to comment on a survey prepared by MHRA on medical devices that may contain material of ovine and caprine origin. No statutory requirement exists for manufacturers or suppliers to provide the MHRA information on these devices and no licensing system operates. A database of approximately 700 products is maintained by the MHRA, of which maybe 100 are currently in use however it is possible for products to exist of which the MHRA is unaware. A new EC directive (EC/2003/32) will require that risk assessments for medical devices are provided to Competent Authorities by the assessment bodies.. The Directive will come into force for new products in April 2004 and retrospectively for existing devices in September 2004.

36. In order to prepare a contingency plan for the possibility that BSE is found naturally occurring in sheep, the MHRA has identified twelve product types containing ovine or caprine materials on the UK market which may present a potential TSE risk to patients. The products are categorised into three groups and assigned an arbitrary and 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). Existing medical device legislation currently regulates the quality and safety of these products.
37. The committee was asked if they had reservations about the arbitrary risk characterisation made for each product type. Members agreed they could not comment on the infectivity of wool although noting that there are no reports of scrapie transmitting to humans. It was noted that anecdotal reports suggest that an early clinical sign of scrapie is a detectable change in the condition of the sheep's wool. Members agreed it was not possible to discount the possibility that TSEs might be present in the Australian sheep flock, but the current opinion was that the risk was, at most, very low. There was no evidence that infected sheep were being used to produce the medical devices, however the committee asked for details of the current Australian testing protocol. Members were informed that the current screening programme for TSEs was an active surveillance program in fallen sheep that used OIE approved numbers, although this remained a small proportion of the Australian sheep flock. Scrapie is not clinically described in Australia, and the last known cases were in an imported flock in the 1950's.
38. The committee agreed that the possibility of transmission of TSE via exposure of wool to tissues was likely to be remote. Members agreed that the risks from these devices would have to be reassessed if BSE were found to occur naturally in sheep. Collagen was provided as an example, where infectivity had not been determined, but which may be a candidate for transmission experiments. Members advised that if such devices were to come into contact with tissues, such as those from the central nervous system (which have a high risk of carrying infectivity), the contact transmission of TSE between open wounds were a relatively efficient method of infection. In these circumstances, the use of this device would have to be re-assessed.
39. The Chair concluded that the committee agreed with the assumptions made in the paper.

Item 6 - Revision of ACDP/SEAC guidance on TSE agents: Scrutiny of Part 1 and Annex C and F of the guidance (SEAC paper INF/80/9)

40. The Chair welcomed Professor Jeffries, Chair of the ACDP/SEAC Joint Working Group (JWG). In June 2003 the JWG published the first tranche of the revised guidance on safe working with TSEs in experimental and clinical settings. This guidance was an update on that first published in 1998. Professor Jeffries explained that since June 2003, three further sections of the guidance had been completed and endorsed by the JWG and ACDP.

41. Professor Jeffries outlined the revisions in part 1 and annexes C and F. Part 1 provides an introduction to the JWG TSE guidance and had been re-drafted for a non-technical audience, and to include scientific developments. Web links to the WHO, Defra, and the National CJD Surveillance Unit had also been included. Annex C covers issues of decontamination and waste disposal. Part 3 of the guidance, which had been previously endorsed by SEAC, is pending publication until annex C was available for guidance on the decontamination of low risk clinical waste. Annex F provides guidance on the use and decontamination of endoscopes.
42. Members were invited to consider the revised Part 1, and annexes C and F. The committee were informed that they would no longer be consulted on the remaining parts of the guidance as the JWG had now been formally decoupled from SEAC but would continue to report to the ACDP.
43. Members informed Prof. Jeffries of a paper³ reporting that sodium hydroxide (0.1M NaOH) treatment of scrapie hamster brain homogenate permitted proteinase K digestion of the resistant PrP^{Sc}. Prof. Jeffries commented that the Working Group would consider the data. However the use of 0.1M NaOH in a healthcare setting posed health and safety concerns, and a rigid adherence to the recommended cleaning protocols remained the most efficient means of minimising transmission of prion disease.
44. The Committee endorsed the revised guidelines and recommended that they be submitted to DH Ministers for publication.

³ : Kasermann F, Kempf C. Sodium hydroxide renders the prion protein PrP^{Sc} sensitive to proteinase K. J Gen Virol. 2003 Nov;84 (Pt 11):3173-6.