



SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

Draft minutes of the 77th meeting held on 11th February 2003

At

Department for Trade and Industry
Conference Centre
1 Victoria Street
London

Members:

Professor P. Smith (Chairman)
Professor J. Ironside (Deputy Chairman)
Professor R. Anderson
Professor C. Bostock
Professor G. Bulfield
Dr D. Cunningham
Mr P. Jinman
Professor H. Kimbell
Professor C. Masters
Dr J. Safar

Technical Advisors:

Mr P. Soul	(Defra)
Dr P. Barrowman	(Defra)
Dr J. Stephenson	(DH)
Ms A. Conroy	(FSA)
Dr S. Dixon	(FSA)

Observers:

Dr A. Allman	(BBSRC)
Dr K. Finney	(MRC)
Dr S. Baxter	(SEERAD)
Dr P. Christie	(SEERAD)
Dr P. Crook	(EA)
Dr A. Douglas	(DARDNI)
Dr J. Nielson	(HSE)
Dr M. Simmons	(NAWAD)
Dr D. Matthews	(VLA)
Mr D. Carruthers	(FSA)
Dr I. Hill	(FSA)

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

Secretary: Dr C. Boyle

Secretariat: Dr R. Pugh
Mr M. Pemberton
Dr C. Ravirajan

Also in attendance: Professor C. Donnelly (Paper 77/8)
Mr P. Comer (Paper 77/8)
Professor D. Jeffries (Paper 77/9)

Item 1 - Chairman's introduction

- 1.1 The Chairman welcomed Professor Christl Donnelly from Imperial College London and Mr Philip Comer from DNV Consulting, who were attending as guests, and Professor Don Jeffries, the Chairman of the ACDP/SEAC TSE Joint Working Group (JWG).

Item 2 - Approval of 14th November 2002 confidential draft minutes (SEAC 77/1)

- 2.1 Members considered the confidential draft minutes of the 14th November 2002 meeting, which were accepted as the final version.

Item 3 - Revision of ACDP/SEAC Guidance on “Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection” (The TSE Guidance): Scrutiny of Parts 3 and Annex D of the Guidance (SEAC 77/7)

- 3.1 The Chairman welcomed Professor Jeffries, Chairman of the ACDP/SEAC Joint Working Group (JWG). In 1998 the JWG published guidance on safe working with TSEs in experimental and clinical settings. Professor Jeffries explained that the 1998 guidance was still in place, but particular sections of the guidance had been revised by the JWG to take account of scientific developments.
- 3.2 Professor Jeffries outlined the revisions in Part 3 and Annex D to the Committee. It was expected that SEAC would be consulted on the remaining parts of the guidance at forthcoming meetings.
- 3.3 The Committee was informed that the guidance had been drafted with a target audience of those responsible for devising local policies. Professor Jeffries explained that parts of the text had been highlighted to signpost the reader to relevant key documents and that infoboxes had been added to the text of Part 3 of the guidance.
- 3.4 Members were invited to consider the revised Part 3 on Laboratory Containment and Control Measures, together with the new Annex on Transport. In addition, providing that the ACDP accept the revised guidance at their meeting in March, Members were asked to agree that the revised guidance could be recommended to Health Ministers and the Health & Safety Commission for publication.

Part 3 - Laboratory Containment and Control Measures

- 3.5 Members suggested amending the first paragraph under the section on Neuropathology to be more explicit, since formalin-fixed tissue is known to, rather than may, retain infectivity. Members expressed concerns about the handling of formalin fixed non-formic acid treated material for

histology, which according to the revised guidance should be handled with the same precautions as fresh material. It was understood that dispersal in the air of microscopic fixed tissue fragments could occur but that practical problems could arise if section cutting of formalin fixed embedded tissue was required to be done in a microbiological safety cabinet, as aerosol dispersal of infected embedded tissue could occur. Members were informed that although no general concerns had been raised regarding air borne dusts in this context, where specific concerns did exist, some workers had worn facemasks or visors. Professor Jeffries explained that more emphasis was being placed on undertaking detailed local risk assessments. Members were also directed to paragraph 3.20 which provides further information on controlling such risks.

- 3.6 The Chairman asked how the data provided by the VLA in the first infobox would feed into a risk assessment, and whether the data provided could be related to a containment categorisation. Professor Jeffries acknowledged that the information presented in the infobox would not necessarily allow accurate definition of containment levels at a local level. The data provided by the VLA related to the results of testing under the active surveillance programme, and hence provides information on the prevalence of infection in a population (cattle or sheep) being studied. Dr Matthews stated that this information would therefore be useful in allowing laboratories to estimate the likelihood of encountering a hazard when working with different animal populations. It was suggested that the infobox would be better placed in the section dealing with diagnostic laboratories.
- 3.7 Regarding the section on parturition, Members asked whether separate guidance existed for assistance at parturition. The Committee was informed that separate guidance did not exist, however the point was noted and would be taken into account.

Annex D - Transport of TSE Infected Material

- 3.8 Members required clarification relating to paragraph D.27 on the transport of small live animals, and whether the comment about mice transmitting TSEs through biting and scratching was evidence based. The Committee was informed that although not based on any specific experimental evidence, conjunctiva or skin abrasion could represent potential sites of entry. Also, as external contamination of the fur could occur following inoculation, the measures were regarded as a reasonable precautionary measure.
- 3.9 In relation to the section on 'classification', Members asked how an established cell line, infected with a TSE, would be classified. Members queried whether it would be treated as equivalent to tissues being transported for diagnostic or investigation purposes. Dr Neilson agreed to consider this particular issue.

Action: Dr Neilson

Conclusion

- 3.10 Subject to the suggested amendments, the Committee endorsed the revised guidelines and recommended that they be submitted to DH Ministers for publication.

Item 4 – Over Thirty Months Rule Review – modelling work undertaken by Imperial College and DNV Consulting (SEAC 77/8)

- 4.1 The Chairman introduced the item by briefly explaining the purpose and background to the presentations by Professor Christl Donnelly of Imperial College London and Mr Phillip Comer of DNV Consulting. No conflicts of interest were declared.

Presentation by Dr Christl Donnelly of Imperial College

- 4.2 Professor Donnelly presented the Committee with updated results of the modelling work to estimate the number of infected animals entering the food supply in GB. In addition, the preliminary estimates of numbers of infected animals that would enter the food supply in Northern Ireland were also presented.
- 4.3 The results utilised the DNV historical exposure estimates to translate the back-calculation model results, presented to the Committee in November 2002, into bovine ID₅₀ estimates. The results also take into account the effect of screening (with a BSE test) all animals over the age of 30 months and the changes in SRM controls over time. To demonstrate the effects of changing the control measures, the level of risk was expressed as a proportion of total exposure during the BSE epidemic.
- 4.4 Using the same scenarios as previously presented to the Committee in November 2002, the analysis showed outcomes in terms of the number of ID₅₀s entering the food supply depending on the sensitivity profile of the diagnostic BSE test employed and the duration of differential mortality assumed for BSE-infected cattle. The modelling assumed an exponential increase in infectivity as animals become closer to clinical onset, with a default of a two-month infection doubling time. Professor Donnelly presented the impact of possible options for changing the OTM rule, which were i) older age thresholds, and ii) birth-date based thresholds.
- 4.5 Results from an analysis based on a test sensitivity profile of 100% sensitivity in the last three months of the incubation period (i.e. little sensitivity more than 3 months prior to disease onset) and a differential mortality in the last three months before onset were presented. The

analysis showed a proportionate increase in the number of bovine ID₅₀s entering the food supply at each increment of age threshold. A similar overall trend was reported when considering a birth-date-based threshold. Members noted that for all of the options presented the overall level of risk levelled off over time due to the assumption of a constant ongoing feed risk. The analysis showed that the highest estimate of the number of bovine ID₅₀s to enter the food supply was approximately 20. This number would increase to approximately 23 if casualty animals were allowed into the food supply.

- 4.6 The Committee was informed that increasing the infectivity doubling time from two months to four months would result in higher estimated absolute levels of risk. This was demonstrated by the presentation of equivalent results using a four month doubling time. The effect of screening was also demonstrated to the Committee by the presentation of equivalent results without screening, which showed that under a plausible scenario, screening eliminates 95% of the risk.
- 4.7 The Committee was also presented with results for i) the most pessimistic scenario considered i.e., a test sensitivity profile of 100% sensitivity in the last three months of the incubation period and a differential mortality in the last twelve months before onset, and ii) the most optimistic scenario considered i.e., a test sensitivity profile of 100% sensitivity in the last twelve months of the incubation period and a differential survivorship in the last three months before onset. Under the most pessimistic scenario, screening would remove approximately 78% of risk, whereas under the most optimistic scenario, screening would eliminate 98% of risk.
- 4.8 It was stressed that it was important to consider the results in the context of the past epidemic. SRM controls were estimated to reduce the exposure to risk by greater than 90%. By considering the proportion of exposure during the epidemic and assuming a very pessimistic scenario of 5,000 vCJD deaths over the next 60 years, the results presented would equate to 0.01 deaths arising from infections occurring over the period 2003 – 2009, albeit with a 100-fold uncertainty.
- 4.9 Professor Donnelly then presented the preliminary results of work to estimate the number of infected cattle that would enter the food supply in Northern Ireland. Members were informed that 1,847 clinical cases had occurred in Northern Ireland by the end of 2002. During 2001/02, 27,329 apparently healthy animals had been tested, of which one had tested positive. During the same period, 35,622 risk animals (casualty, fallen stock and emergency slaughter) had been tested, of which 98 had tested positive. The source of the data used for the analysis was the APHIS tracing system, which contained the records of 9.6 million cattle in Northern Ireland. Statistics relating to the total number of risk animals by year were not available, so the proportion of total animal deaths which resulted in casualty or fallen stock as a function of age was assumed to equal that estimated for Great Britain.

- 4.10 The Northern Ireland epidemic through time was presented by birth cohort. Members noted that the epidemic had dropped to its lowest level in 1999, with a subsequent increase in numbers of BSE cases. This differed from the position in GB and it was suggested that it may reflect a change in case ascertainment due to the introduction of screening. The screening results for apparently healthy animals and risk animals between GB and Northern Ireland were very similar.
- 4.11 The preliminary results of infection incidence over time, based on a test sensitivity profile of 100% sensitivity in the last three months of the incubation period and a differential mortality in the last three months before onset, indicated very poor case ascertainment. 92% of animals that would have otherwise become BSE cases were estimated to have suffered differential mortality with 93% of those dying as risk animals. The Committee was presented with an analysis of the results relating to i) the number of animals entering the food supply in the last 12 months of incubation, and ii) infectivity exposure expressed as ID₅₀s entering the food supply. Members noted that, under the same range of options, the risk (in terms of the absolute level of ID₅₀s) in Northern Ireland was estimated to be ten-fold less when compared to GB – though it should be noted that the total size of the NI herd is roughly ten fold less than the GB herd. Overall, the relative effect of policy changes to the OTM rule would be very similar for Northern Ireland as for GB.
- 4.12 The Chairman emphasised the point that even under extreme options such as completely abandoning the OTM rule, the risk of future exposure was significantly less than the risk of exposure in the past. In view of this point, Members asked whether any cost assessments were being undertaken to consider the different options for changing the rule. Mr Carruthers of the FSA explained that the FSA Core Stakeholder Group was considering cost, practicality and enforceability of the various options. The cost of the Over Thirty Months Scheme was approximately £380 million per annum.
- 4.13 Members asked about cost of screening per animal. Dr Matthews of the VLA explained that it would be difficult to estimate since the industry would be expected to contribute to certain costs. Further, although all animals over the age of thirty months entering the food supply are currently required to be tested under the Commission's surveillance programme, the targets for testing would be reviewed once two years worth of data had been collected. It is possible that the Commission may re-focus their attention to testing risk animals only, in which case, industry would have to decide whether testing should continue for other animals entering the food supply.

Presentation by Mr Phillip Comer of DNV Consulting

- 4.14 Mr Comer presented an update on the work undertaken by DNV Consulting for the FSA in relation to the review of the OTM rule. This

was an update of the work presented to SEAC at their meeting in November 2002 which examined the possible exposure to BSE infectivity by considering the infectivity present in different tissues that could enter the human food supply.

- 4.15 Mr Comer reiterated that the main route of recent exposure to infectivity related to DRG, which accounted for 90% of the exposure. In addition to the potential routes of exposure presented at the November 2002 meeting (see table at paragraph 4.28 of the closed session minutes for SEAC 76) the effect of SRM control failures had now been taken into account. During the period 1998 – 2000, 12,000 inspections had been undertaken of which seven unsatisfactory reports related to SRM. In terms of calculating exposure from SRM failures, this was estimated at 0.0007 bovine oral ID₅₀s.
- 4.16 The three main sources of historical exposure were mechanically recovered meat (MRM), head meat and direct consumption of brain. Members were informed about the likely level of infectivity from these three sources.
- 4.17 The total exposure to infectivity from one fully infected bovine slaughtered for food for each of the years 1980 to 2001 was presented to the Committee. For adult animals (over the age of two years) the major contributor to exposure to infectivity was MRM, which was prohibited in 1995. The contribution from brain and head meat remained relatively steady, until both products were prohibited in 1989 and 1996 respectively. For prime beef animals, the dominant contributor up to 1989, when it was classified as SBO, was brain. Unlike MRM and headmeat, which would have been distributed widely in products such as minced meat and burgers, the consumption of brain is likely to have been focused on a smaller number of people. Members were presented with the data in the form of a time series graph showing the historical exposure estimates for adult animals and prime beef animals expressed as bovine ID₅₀s entering the food supply. This analysis highlighted the impact of the various controls introduced over time.
- 4.18 Members asked how the assumptions for the SRM control failures were derived. They were informed that the 5% relating to spinal cord left on the carcass was estimated from the actual inspection failure case, but the 10% estimate relating to the spinal cord entering the food supply was an estimate. Despite this, the contribution from SRM failures would be insignificant.
- 4.19 Members suggested plotting the upper confidence bounds on the time series graph showing the historical exposure estimates. The analysis showed the median current exposure level for a fully infected animal entering the food supply as 27 bovine ID₅₀s, with an upper confidence bound of 240 bovine ID₅₀s. It was agreed that plotting the upper confidence bounds would be useful.

- 4.20 Members asked if the next generation of assays would impact on the modelling work given that they are reported to be three to four logs more sensitive than the current screening assays. Members were reminded that the modelling had considered test sensitivity profiles ranging from 100% sensitivity in the last three to twelve months, so any improvement in test sensitivity was included in the scenarios examined. The Chairman explained that the view of the joint FSA / SEAC Risk Assessment Group (RAG) was that the test sensitivity profile with 100% sensitivity in the last 12 months before onset, as considered by the modellers, was better than the performance of current tests.
- 4.21 Members asked if animals with sub-clinical infection would enter the food supply. The Chairman commented that the modelling takes account of pre-clinical cases. However, if sub-clinical infection is defined as those animals that are infected, but would never go on to develop the disease, then the modelling did not take account of this form of sub-clinical infection. Professor Donnelly added that if infectivity were present in other parts (permitted under SRM regulations) of such animals prior to detection in the brain, then this was not prevented from entering the food supply by a screening programme. However, she added that there was no evidence to show that this was happening.
- 4.22 Members commented about the reduction in the measured levels of infectivity in BSE affected cattle over the course of the epidemic. The titres of infectivity in BSE affected cattle brainstems have dropped by about two logs from the early 1990s. It was suggested that this may be due to better identification of clinical cases. The Committee was informed that the assumptions relating to the bovine oral infectivity had been derived from the attack rate experiment, which is yet to be completed. Taking into account the interpretation by the Scientific Steering Committee of the original attack rate experiment, a median value of 50 bovine oral ID₅₀/g of brain tissue as the bovine oral infectiousness had been used, with a wide variation.
- 4.23 Mr Harvey of the FSA provided the Committee with an update of the current working timetable for the completion of the review of the OTM rule. A further Core Stakeholder Group meeting would be held in February prior to a wider stakeholder meeting in early March, which would be held in public. A 12 week consultation period was expected to commence at the end of March, with final recommendations being made to the FSA Board in July, following which recommendations would be made to Ministers. Mr Harvey also informed the Committee that, in parallel to assessing the risk from domestic production, work was being undertaken to assess the risk of imports from the Republic of Ireland, which is the largest exporter of cattle to the UK.
- 4.24 The Chairman concluded the discussion by thanking both Professor Donnelly and Mr Comer for their presentations. The work undertaken by Imperial College London was being prepared for submission for

publication and the work undertaken by DNV would be provided to the FSA as a report.

AOB

- 5.1 Dr Matthews provided the Committee with an update from the second attack rate study in cattle and a new result from the ongoing cattle pathogenesis study. In respect of the second attack rate study, it was reported that a second animal had died in the 0.1 gram oral challenge group. Transmission had also been demonstrated to single animals in the 1g and 0.01g challenge groups. For clinical onset, the incubation period ranges from 49 months to 58 months, which was within the range seen for the 1 gram or 10 grams dose group in the previous attack rate study.
- 5.2 The Committee was also informed of the latest result from the ongoing cattle pathogenesis study. As part of the intracerebral challenge study, a group of five animals were challenged with pooled third eyelids collected from ten naturally occurring clinically affected BSE cows. Transmission was confirmed in the first of the group with an incubation period of 33 months; 12 months shorter than the tonsil result previously reported and 10 months longer than animals challenged with brain collected 32 months post-challenged in the original cattle pathogenesis study. Dr Matthews commented that the result was unusual in that it did not appear to fit in with other lymphoid tissue challenges undertaken intracerebrally in cattle, where pooled lymphnodes or pooled spleens had failed to transmit infectivity. A full written report on the finding will be available for the next meeting.
- 5.3 Members asked whether any analogies to third eyelid existed with humans in the context of the risk of human to human transmission. Professor Ironside commented that the issues concerning ophthalmology and ophthalmic surgery and CJD relate more to risks relating to the retina, optic nerve and the cornea rather than lymphoid tissue.
- 5.4 The Chairman agreed that it would be useful for the Committee to receive regular reports of the results from the attack rate study and the pathogenesis study, with a summary at the next meeting on the progress of these studies.

Action: VLA

- 5.5 Dr Matthews commented that he thought SEAC should similarly receive regular updates on the progress of the sheep pathogenesis studies. The Chairman requested the Secretariat to liaise with the VLA and Defra on this issue.

Action: Secretariat