



EIGHTY-EIGHTH MEETING OF THE SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

The Spongiform Encephalopathy Advisory Committee held its 88th meeting in London on 30th June 2005, when it discussed the following matters:

CURRENT ISSUES

SEAC was informed about the following issues:

- Publication on the SEAC website of the committee's statements on (i) a risk assessment on the age of vertebral column as specified risk material and (ii) the early phase of vCJD infection in blood recipients as well as the 2004 SEAC Annual Report.
- Publication on the DH website of a risk assessment of vCJD transmission via surgery and on the MRC website of the Government's TSE Joint Funders Group (JFG) research strategy 2005-2008 (both considered previously by SEAC).
- An invitation for committee members to provide comment as part of a public consultation of the FSA Science Strategy 2005-2010.
- A recent paper¹ reporting a sensitive diagnostic test (conformation dependent immunoassay) for CJD. The committee considered this to be a potentially important test because, unlike most biochemical tests, it did not rely on proteinase K (PK) digestion of prions. It could therefore, detect PK sensitive forms of abnormal prions. It was noted

¹ Safar *et al.* (2005) Diagnosis of human prion disease. *Proc. Natl. Acad. Sci. U S A.* 102, 3501-3506.

that a JFG workshop would discuss advances in diagnostic tests in Autumn 2005.

- The identification of two clusters of three BARB (see later) BSE cases.
- Advice had been sought from the SEAC Chair by Defra about research on historic sheep samples. The Chair had responded that, in his opinion, analysis of these samples should not be rushed. A number of possible questions could be addressed including, genotype-phenotype interactions, whether historically BSE ever entered the sheep flock, and the possible prevalence of atypical scrapie. As Defra is still considering how to proceed, it was emphasised that research questions should be considered carefully before embarking on any studies as the samples were valuable. It was noted that EFSA had recently recommended (08/06/05) that Member States test historical sheep and goat samples to help inform analysis of the phenotype and retrospective occurrence of TSEs.
- Recent analysis by VLA of samples from a USA cow slaughtered in 2004 had confirmed a diagnosis of BSE. The committee noted that initial results from tests carried out in late 2004 had been inconclusive and follow up of the cases had taken a number of months. SEAC was informed that USA BSE surveillance has since been altered to allow rapid confirmatory testing of inconclusive results.

RESEARCH ON ABNORMAL PRIONS IN BOVINE MILK

FSA asked SEAC to consider the findings of research to develop diagnostic tests to detect BSE infection-associated abnormal prion protein (PrP^{BSE}) in cows' milk and to screen milk from cattle experimentally infected with BSE for the presence of PrP^{BSE} . SEAC received a report from the FSA/SEAC Milk Working Group which oversaw the research.

SEAC considered the study to be well designed and carefully conducted. The committee agreed that the study showed no evidence for the presence of PrP^{BSE} in milk from experimentally infected cattle, within the limit of detection of the test methods used. It was noted that only the cellular fraction of milk had been

analysed because previous tissue fractionation studies on prions had shown them to be associated with cell membrane fractions. The committee suggested that, for completeness, the soluble fraction might also be tested although it was recognised that, if it were decided to undertake this work, there would first be a requirement for substantial method redevelopment and validation. It was suggested that the study samples be retained to allow possible future analysis.

SEAC concluded that the results of the study, together with the findings from previous epidemiological and experimental research, provided no evidence for the presence of PrP^{BSE} in, or for transmission of BSE via, milk.

DIFFERENTIAL DIAGNOSIS OF SUSPECT BSE CASES

During previous discussions of UK BSE surveillance (SEAC 84), SEAC noted that there had been a decline in the number of suspect BSE cases, identified on the basis of clinical signs, that were subsequently confirmed when BSE diagnostic tests were applied. As the cause of disease in the unconfirmed cases is unclear, SEAC considered that procedures to identify differential diagnosis of any altered form of BSE would be important. Defra presented its approach to differential diagnosis of BSE to the committee.

Defra noted that there is a very wide range of neurological conditions in cattle thus, it would be unfeasible to reach a definitive diagnosis for all suspect cases of BSE. Furthermore, there was no evidence for BSE strain variation from UK research and surveillance data. Prospective study of variation of BSE would be difficult due to the low numbers of BSE cases for study and the unsuitability of many samples for detailed post mortem analysis.

SEAC recognised the difficulty in obtaining a definitive diagnosis in all cases of neurological disease in cattle. However, SEAC emphasised the need for ensuring that altered forms of BSE were not missed, especially in view of recent studies on scrapie variants in sheep. SEAC suggested that analyses should incorporate a broad range of TSE tests on a wide range of both CNS and peripheral tissues from suspect animals.

SEAC welcomed initiatives, including a training video, to ensure that veterinarians were skilled in the clinical diagnosis of BSE so that cases would not be missed.

BARB CASES

SEAC considered a number of issues related to BSE cases born after the UK reinforced mammalian meat and bone meal ban in August 1996. Around 100 of these BSE cases, referred to as BARB cases, have been reported in the UK. Their cause is unknown.

Sequencing PRNP of BARB cases

Defra asked SEAC to comment on the findings of two studies comparing the sequences of the prion protein gene (PRNP) carried by BARB cases and by healthy control animals in Great Britain and Northern Ireland. This was to examine whether the form of PRNP may have predisposed BARB cases to the disease as occurs in prion diseases of sheep and humans. In the NI study, a further prion-like gene (PRND) was examined and comparisons were made with gene sequences of BSE cases born before the reinforced ban as well as controls.

SEAC noted that neither study had revealed significant differences between the gene sequences of the BARB cases and controls. However, in the NI study a significant difference was found in one region of PRNP when comparing all the BSE cases (born before and after the reinforced ban) taken together and the controls. The committee concluded that on the basis of these studies there is no evidence that a particular form of PRNP or PRND had predisposed BARB cases to the disease.

Response to the SEAC ad hoc Epidemiology Subgroup on UK BARB Cases

At SEAC 87, the committee received a report from the SEAC *ad hoc* Epidemiology Subgroup on UK BARB cases which was advising on the design of a case control study by Defra to identify possible causes of BARB cases. SEAC had endorsed the Subgroup's recommendations for further analysis of the results using different groups of controls, and for prospective evaluation of

animal feed use and supply routes and the potential for cross-contamination of feeds.

SEAC was informed that no statistically significant risks or protective factors relevant to BARB cases had been identified using the new sets of controls. Evaluation of the feed history of BARB cases was ongoing.

Review of the cause(s) of BARB cases

Professor William Hill (University of Edinburgh), commissioned by Defra to review the evidence for causes of BARB cases, gave an overview of his report.

SEAC welcomed Professor Hill's report and agreed it made an important contribution to the discussion on the causes of BARB cases. While SEAC concurred with the main conclusions of the report, members provided Professor Hill with a number of comments to consider before finalising his report.

'This report has now been published on the Defra website and can be accessed via <http://www.defra.gov.uk/animalh/bse/index.html> '

SEAC EPIDEMIOLOGY SUBGROUP MEETING SUMMARY

The Chair of SEAC Epidemiology Subgroup updated the committee on the Subgroup's first meeting to discuss the nature and future profile of the vCJD epidemic. Discussions had focussed on assessment of current infection prevalence, the influence of genotype and age on infection prevalence and the interaction of potential routes of secondary transmission. Work was continuing with a second meeting scheduled in September 2005.

UPDATE ON RESEARCH INTO ATYPICAL CASES OF SCRAPIE

SEAC was updated on research in progress on cases of scrapie that had given unusual (atypical) results in the diagnostic tests used in active surveillance. Close to 100 atypical scrapie cases had been identified in the UK. The item was discussed in a reserved business session because it involved consideration of unpublished research.

SEAC was informed that a formal definition of atypical scrapie had not been agreed but that the EC Reference Laboratory expert group and EFSA were considering a classification. The committee noted the progress made in sequencing elements of the prion protein gene of atypical scrapie cases and of developments in immunohistochemical methods to detect abnormal prion protein in atypical scrapie samples. Transmission studies on samples from atypical scrapie were underway. SEAC agreed that, now that a number of issues around atypical scrapie are becoming clearer, the SEAC Sheep Subgroup should consider the available scientific information in more depth, and new data immediately it becomes available, because of possible implications for the National Scrapie Plan.