



INDEPENDENT REVIEW OF THE ORIGIN OF BARB CASES

ISSUE

1. To comment on an independent review of Defra research on the cause(s) of BARB cases (BSE cases Born After the UK Reinforced Ban in 1 August 1996).

BACKGROUND

2. On 31 July 1996, additional BSE control measures to restrict the recycling of animal protein in animal feed were introduced to include a total ban on the sale or supply of any mammalian meat and bone meal (MMBM) or any feedstuff known to include MMBM. Following a recall scheme for feed containing MMBM, it also became an offence from 1 August 1996 to possess feed for farmed livestock containing MMBM. A similar ban was instituted across the EU on 1 January 2001. Despite these control measures there have been around 100 cases of BSE detected in cattle born after the reinforced ban in the UK.

PREVIOUS SEAC CONSIDERATION OF BARB CASES

3. In 2003, SEAC considered data on BARB cases as well as the possible causes/origins of BARB cases including:
 - Residual cross contamination of feed as a source of infection,
 - A maternally associated risk factor for infection,
 - Other sources of infection, e.g. scrapie agents,
 - Non-feed routes of transmission e.g. via contaminated soil or water,
 - Infection associated with an enhanced genetic susceptibility to low levels of exposure to the infectious agent,
 - A spontaneous occurrence of BSE in cattle,
 - Horizontal transmission occurring from unidentified carriers.
4. On the evidence presented, SEAC agreed that residual feed contamination with the BSE agent seemed to be the most plausible explanation for BARB cases. It was noted that this

contamination might be due to the use of imported feed materials from EU countries that had not implemented feed controls similar to those in the UK, until 2001¹. However, the committee considered that other possible routes of transmission such as maternal or environmental transmission could not be excluded as being possible origins of at least some of the cases. The committee suggested a number of areas of research including genotyping, biochemical and strain typing studies of BARB cases. In addition, a SEAC *ad hoc* Epidemiology Subgroup on UK BARB cases was convened to advise on the design of a case-control study to examine hypotheses for the source of infection in BARB Cases to be conducted by Professor John Wilesmith (Defra).

PROFESSOR HILL'S REVIEW

5. In November 2004, Defra commissioned Professor William Hill (Institute of Evolutionary Biology, University of Edinburgh) to examine the BARB studies currently taking place (see Annex 1). As part of the review Professor Hill discussed the possible causes of BARB cases with the committee at SEAC 86 (see Annex 2). He also attended the April 2005 meeting of the SEAC *ad hoc* Epidemiology Subgroup on UK BARB cases. A report of the Subgroup meeting was provided to the committee at SEAC 87 (see Annex 3).
6. Professor Hill has completed his review. A report is given at Annex 4. Please note Annex 4 has not been circulated outside of the committee. This is at the author's request as the report contains new scientific data that have not yet been published in a scientific journal. As premature release of unpublished data may prejudice publication, the report has not been released more widely in hard copy prior to publication (this is in accordance with SEAC's code of practice). However, the author is content for the committee to discuss the report in the public meeting.

ADVICE SOUGHT FROM THE COMMITTEE

7. The committee is invited to comment on Professor Hill's report.

¹ The European Union's Scientific Steering Committee (SSC) came to a similar conclusion in an opinion published in 2003: http://europa.eu.int/comm/food/fs/sc/ssc/out353_en.pdf

DEFRA PRESS RELEASE ANNOUNCING HILL REVIEW

**INDEPENDENT EXPERT TO REVIEW DEFRA'S WORK ON BSE
CASES BORN SINCE 1 AUGUST 1996 IN THE UK**

Professor William Hill FRS, Emeritus Professor at the Institute of Evolutionary Biology, School of Biological Sciences of the University of Edinburgh has been appointed by Defra to carry out an independent review of their work on BSE cases born since 1 August 1996 in the UK.

The Chief Veterinary Officer, Debby Reynolds said, "I am delighted that Professor Hill has agreed to undertake this review for us. There has been enormous progress in reducing the number of cattle infected with BSE in the UK since the first case was found in 1986. Much of this can be attributed to the controls that were put in place to prevent the spread of the disease in meat and bone meal, an ingredient that was used extensively in animal feed prior to 1988. These controls have gradually been tightened over ensuing years and in the UK particularly so since 1 August 1996.

Despite this we have had 99 cases of BSE born since 1 August 1996. The current advice, which has been considered by both SEAC and a European scientific advisory committee, is that feed contamination still remains the most plausible explanation, as the feed controls in some parts of Europe were not introduced until 2001. We have work in place to test this theory. However, there are also other possible explanations for at least some of these cases. We want to eradicate this disease and it is important for us to be sure that we are not overlooking any important factors and that the work we are doing is comprehensive and scientifically sound.

We have therefore invited Professor Hill to take a look at what we are doing. We have deliberately chosen someone who is eminent in his own field but who has not been involved in TSE work before. He can be expected to probe and challenge the evidence. If we can meet this challenge it will give us reassurance that we have not overlooked anything that might prevent us from getting rid of the disease by the end of 2010. If we have overlooked something it will give us time to put in place some additional studies.

I have asked Professor Hill to report his findings to me within the next six months and I will ask SEAC to consider these."

23 November 2004

Notes for editors

1. Professor William Hill OBE, BSc, MSc, PhD, DSc, FRSE, FRS is Emeritus Professor of Animal Genetics at the School of Biological sciences of the University of Edinburgh. His group undertakes theoretical and experimental studies on population and quantitative genetics and on their application to animal improvement. Professor Hill was formerly Dean and Provost of the Faculty of Science and Engineering at the University of Edinburgh, he has consulted extensively in the UK animal breeding industry and chaired Defra's National Consultative Committee on Animal Genetic Resources. He is also an editor of Genetical Research and senior editor designate of Proceedings of the Royal Society, Series B.

2. The hypothesis that cases born after the reinforced feed ban (BARBs) are due to an exogenous feed source arising from the perfectly legal handling and shipment of meat and bone meal in European ports up to January 2001 comes from John Wilesmith following a detailed analysis of epidemiological data on the first 59 cases. This analysis has been considered by the EU's Scientific Steering Committee and more recently by EFSA.

3. A SEAC ad-hoc group is overseeing a case control study the primary objective of which is to test this hypothesis. In addition Defra is funding work to investigate the genetic homogeneity of the PrP gene in BARB cases. Professor Hill will consider all of this work as part of his remit.

4. Further details of the legislation in place relating to feed controls and information on BARB cases can be found on the Defra website at www.defra.gov.uk/animalh/bse/controls-eradication/feed-ban.html.

ANNEX 2

Extract from SEAC 86 minutes

ITEM 4 – INDEPENDENT REVIEW OF ORIGINS OF BARB CASES (SEAC 86/3)

1. The Chair explained that in November 2004, Defra commissioned Professor William Hill (University of Edinburgh) to carry out an independent review into the cause of BARB cases (BSE cases born after the reinforced meat and bone meal ban was introduced in 1st August 1996). Professor Hill had asked to consult SEAC on the scope of the review. SEAC would be asked to comment on the findings of the review once completed. To date 93 GB BARB cases had been identified. In previous discussions, SEAC had agreed that the most likely hypothesis for BARB cases was most likely to be due to feed contaminated in transit prior to the EU-wide feed ban. However, the SEAC ad hoc Epidemiology Subgroup on UK BARBS was involved in a case-control study to examine possible origins of BARB cases. The Subgroup would meet in April 2005 and report interim findings of the study to SEAC at the next meeting.
2. Mr Mike Prince (Defra) updated the committee on the most recent BARB case, identified as part of the TSE surveillance that had been born in October 2001. Although the farm of origin had a history of BSE (a total of 6 cases), the last case occurred in 1994. The case was noteworthy because the animal had been born after the EU-wide feed ban (January 2001). The rations fed to the animal were under investigation. The case would be considered by Professor Hill as part of his review.
3. Professor Hill asked SEAC whether there were issues that should be considered as part of his review that he may not already have identified. It was clear that the clinical signs, neuropathology and age of onset of BARB cases were similar to that of BSE cases born before the feed bans. The geographic distribution of BARB cases appeared to be random, although three pairs of cases with the same farm of origin had been identified. BARB cases occurred almost entirely in dairy cattle. Causes of BARB cases that would be considered included: contaminated feed derived from European sources before the EU-wide ban in 2001; maternal transmission of BSE (although this could not explain the origins of all BARB cases); environmental causes; and a possible genetic disposition to the disease. Other hypotheses that would be considered

included organophosphate use and the presence of toxic alkaloids in types of grass.

4. Professor Hill was informed about an EU-funded project looking at possible links between environmental minerals and TSEs. As part of the project, geographical maps were under development showing the concentrations of bioavailable minerals. The geographical distribution of BARB cases and minerals could be compared.
5. It was noted that the incidence of BARB cases was similar to that of sCJD. A member asked whether there might have been a low background level of BSE prior to the epidemic. Professor Hill considered that pre-1970, cases of BSE should have been reported by vets if it was of a similar prevalence to BARB cases. However, members noted that a possible confounding factor in such historical analyses might be the number of animals that present with BSE-like clinical signs that are subsequently not confirmed as BSE cases on post mortem. Historically, the post-mortem level for animals was very low and thus, it would not be possible to determine the level of historical BSE cases. Professor John Wilesmith (Defra) added that modelling work suggested that, under the conditions prior to the feed bans, even a single case of BSE might rapidly give rise to an epidemic.
6. Members asked whether data were available from BSE-free countries with TSE surveillance programmes that may inform assessment of a possible background level of disease. Professor Wilesmith explained that a project was underway to model TSE surveillance in other countries that could provide such data. Members considered it important to focus surveillance on casualty animals as surveillance in this group was most likely to detect an endemic disease.
7. The Chair suggested that Professor Hill contact the Advisory Committee on Animal Feedstuffs (ACAF) as that committee was carrying out a detailed survey of the enforcement of animal feeds. Members noted that the distribution of animal feed was extremely complex.
8. Dr Jim Hope (Veterinary Laboratories Agency) informed the committee of a recent Defra-funded project to sequence the PrP gene of BARB cases and control animals matched for breed and birth cohort. To date, the open reading frame of the PrP gene had been sequenced but preliminary results indicated there were no significant differences in the sequence of the PrP gene between

the two groups. The committee welcomed such data and asked that the study be completed as rapidly as possible.

9. Members recommended that infectivity studies on samples from BARB cases should be conducted but acknowledged that samples of sufficient quality may be difficult to obtain.

ANNEX 3

Extract from draft SEAC 87 minutes

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

1. 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.
2. 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.
3. 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.
4. 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.

5. 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.
6. 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.
7. 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.

8. 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.