



TERMINATION OF TISSUE INFECTIVITY ASSAYS IN CATTLE

Issue

1. To note the proposed termination of cattle bioassays of BSE infectivity and comment on the scientific rationale.

Background

2. The FSA funds two projects (originally commissioned by MAFF in 1996) to detect the infectivity in bovine tissues from cattle inoculated with BSE using cattle bioassays (MO3006/3007). Cattle bioassays have been demonstrated to be 500 times more sensitive than the traditional mouse bioassays previously used to determine bovine tissue infectivity. Neural and non-neural tissues collected from cattle at a number of time points following oral challenge with 100g of BSE brain homogenate are being tested using the cattle bioassay.
3. As reported to SEAC previously, infectivity has been confirmed in cattle bioassays of pooled CNS tissues sampled from cattle 32 months post oral challenge and in pooled distal ileum sampled from cattle 6, 10 and 18 months post oral challenge. These findings were consistent with the results from previous mouse bioassays of these tissues. In contrast to the findings from mouse bioassays, infectivity was also detected, by cattle bioassay in tonsil tissue collected 10 months post oral challenge. Clinical signs were observed in 1/5 animals in the tonsil tissue challenge group. Clinical onset is estimated to be at 45 months.
4. In addition, infectivity has been detected, by cattle bioassay, in a pool of lymphoid tissue from the nictitating membrane collected from natural cases of BSE. One animal was killed 33 months p.i. (post inoculation) following clinical progression of disease.
5. The initial challenge groups are now reaching 8 years p.i. and the original proposal to MAFF indicated that 7 years p.i. may be the anticipated end point for the study.

Termination of the study

6. FSA is now planning to terminate the cattle bioassays based on a consideration of the financial and animal welfare implications of continuing the studies together with a consideration of the possible data that may be lost from terminating the studies. The large animal studies comprise 70% of the Agency's current expenditure on TSEs. As the BSE epidemic in cattle is in decline, the FSA research spend will be redirected to high priority issues. To accommodate a 15% year on year reduction in the FSA's TSE research budget a refocus of funds is necessary, away from the funding of large animal studies to research into non-invasive live animal TSE diagnostic tests outlined in the FSA strategic plan for 2005-2010.
7. In addition, although VLA has considerable experience of the practicality of keeping cattle on experimental studies for periods of up to 10 years, there are animal welfare implications to consider in keeping animals for extended periods of study. For example, lameness resulting from joint diseases has been a cause of culling in the past. Thus, this could lead to the possibility of reduced group sizes, the longer experiments are allowed to run.
8. The mid-term review of the FSA TSE research programme was held in June 2004. The independent scientific review panel recommended that the ongoing cattle to cattle bioassays be terminated at an endpoint to be determined from a review of bioassay titration studies plus a margin to account for the known variability of the assay. The paper at Annex 1 sets out the scientific justification for ending the current studies at 7 years p.i..
9. The paper by Wells *et al* (Annex 1) uses data from titration studies performed in cattle and mice to produce a model of the mean incubation period in months related to the infectious dose in mouse ic/ip LD₅₀ / g of tissue. The analyses provided indicate that, with a wide margin, a termination of the studies at approximately 7 years p.i. will not result in any measurable loss of data on the infectivity of tissues under assay.
10. A culling strategy is planned to start in November 2004 and be completed in March 2007 as each of the challenge groups reaches the stage of 7 years p.i.. A series of tissues will be collected and tested to determine the presence of abnormal prion. The tissues will include brain, spinal cord (cervical, thoracic and

lumbar), distal ileum Peyer's patches and tonsil. This is based on the current knowledge of peripheral involvement in cattle, and on the results from the parenteral challenge of pigs, with BSE.

Advice sought from the Committee

11. Members are invited to note the planned termination of this study and comment on the scientific rationale.