ANNEX B

SUMMARY OF RESEARCH INTO THE TRANSMISSIBILITY OF SCRAPIE TO CATTLE

Early Stages

1. On 21 June, 1988 **(YB 88/6.21/5.1-5.2)** Professor Southwood wrote to the Permanent Secretary, Mr D Andrews, to bring a number of matters to his attention. One of these was the Southwood Working Party's belief that tests should be undertaken on cattle with meal known to be infected with scrapie. Professor Southwood stated that this would test the hypothesis that infected meal was the origin of BSE.

2. In September, 1988 **(YB 88/9.26/5.1)** the Chief Veterinary Officer submitted a paper on the BSE research programme to Professor R Bell (the MAFF Chief Scientific Advisor) for the Minister's PES meeting with the Treasury. In this document, a brief outline of an experiment to determine whether cattle are susceptible to natural sheep scrapie was given, together with manpower and cost requirements over five years. Although the paper acknowledged that specific accommodation would be required, this was not included in the costs. The paper assumed that the natural scrapie inoculum would be provided free of charge by the NPU.

3. In November, 1988 **(YB 88/11.17/2.1-2.4)** the CVO held a BSE R&D meeting with representatives from MAFF (Dr Watson, Mr Bradley, Mr Atkinson and Mr Dawson) and the IAH (Professor F Bourne, Dr J Hope, Dr H Fraser and Dr D Taylor). The scrapie to cattle transmission experiment was discussed and given a lower priority as a similar experiment had been carried out in the USA. It was agreed that the transmission of natural scrapie to cattle should be carried out by the CVL and that the mouse bioassay should be conducted at the NPU.

4. In February, 1989 **(IBD 1 Tab 2)** the Southwood report was published. Although the report referred to the need to consider transmission studies in a variety of host species and stated "parallel cattle studies are also planned using the scrapie agent" (paragraph 8.5.2), the report did not specifically recommend any studies on the transmission of scrapie to cattle.

5. In June, 1989 **(IBD 1 Tab 4)** the Tyrrell Committee submitted their interim report to the Government. The report recommended epidemiological studies on the incidence of spongiform encephalopathy in species known to be susceptible (sheep, goats and mink) with particular emphasis on possible recent changes of scrapie in sheep. The report stated that it remained uncertain how relevant the recent suggested increase in sheep scrapie had been for the emergence of BSE and that the results of research in progress and proposed could have a bearing on the measures adopted to deal with scrapie in sheep. The report did not recommend any studies on the transmission of scrapie to cattle.

6. In May, 1990 **(J/AVMA/196/1679)** a paper was published in the Journal of the American Veterinary Medical Association detailing work on the transmission of scrapie to cattle initiated by the USDA at Mission, Texas, in January, 1979. In this study, ten calves were each challenged intracerebrally, orally, intramuscularly and subcutaneously with scrapie which had been subpassaged in either a sheep or a goat. Three of these animals went on to develop clinical symptoms of a spongiform encephalopathy which differed from those seen with BSE infection. PrP was detected in tissues from these cattle, but neurohistologically the changes seen in the brains from these cattle were consistent with scrapie and differed from BSE. Material from the affected cattle was bioassayed in mice which were observed for 2 years. The mice remained clinically and neurohistologically negative apart from one group which, although they showed CNS signs, were histologically negative.

7. On 30 October, 1990 **(YB 90/10.30/1.1-1.6)** a joint NPU/CVL BSE R&D meeting was held at the NPU in Edinburgh. The meeting was attended by Mr Bradley, Mr Wells, Mr Wilesmith, Dr Wrathall, Mr Dawson, Mrs Deakins, Dr MacOwan, Dr Jeffrey, Dr Bostock, Dr Hope, Dr Fraser, Dr Bruce, Dr D Taylor, Dr Sommerville, Dr Hunter and Mr Maslin. Mr Wilesmith proposed that a parallel pathogenesis study of scrapie to cattle should be conducted with the objective of studying the comparative pathogenesis. The meeting considered that the susceptibility of cattle to scrapie was of some importance. The experiment would require the inoculation of scrapie to cattle. It was agreed that Mr Bradley should seek the views of the Tyrrell Committee on the project.

8. At the SEAC meeting in November, 1990 **(YB 90/11.01/7.1-7.9)** the committee only supported pathogenesis studies in cattle in principle because of concern over the number of animals and gave no support to BSE pathogenesis studies in sheep. On receipt of the minutes of this meeting, on 16th November, 1990, Dr MacOwan wrote to Dr Shannon and Dr White expressing his concern over SEAC's reservations about these proposals and stating that feeding scrapie infected brain to cattle could shed light on whether or not BSE arose from scrapie infected meat and bone meal **(YB 90/11.16/13.1)**. On 19th November, 1990 in response to a query from Dr Shannon, Dr MacOwan indicated that to the best of his knowledge there was strong support for pathogenesis studies from both the CVO and CVL **(YB 90/11.19/2.1)**.

9. On 28 November 1990 **(YB 90/11.28/9.1)**, Mr Bradley wrote to the CVL/NPU project leaders, attendees of 30 October, 1990 NPU/CVL meeting, including Mr J Maslin and Dr MacOwan, Dr Shreeve, Dr Little and Mr Lowson to inform them of the view of the Tyrrell Committee on various proposed experiments. In this minute, Mr Bradley stated that the proposed experiment on the pathogenesis of scrapie in cattle had not been supported. He maintained that the committee could see no point in it as the attack rate could not be estimated and that they considered it to be too expensive in resources. He went on to state that the committee considered the objective of a comparative pathogenesis study to be inappropriate.

10. In the minutes of the March 1991 SEAC meeting it is stated that the study of scrapie pathogenesis in cattle and the transmission of natural scrapie to cattle by the oral route would not be pursued **(YB 91/3.07/4.1-4.9)**.

Later stages

11. On 9 February, 1993 **(YB 93/2.09/1.1-1.4)** a meeting was held at Tolworth at the request of the CVL to discuss views on research proposals and to indicate policy needs. Mr Lowson, Mr K Taylor, Mr Bradley, Dr MacOwan, Mr Jenkinson, Mr Wilesmith, Mr Wells, Mr Dawson, Mr Jeffrey, Mr Maslin and Mr Dixon attended this meeting. An experiment to challenge cattle with scrapie intracerebrally was discussed. It was stated that from the policy viewpoint, this study was of academic interest only, in light of the measures already in place for BSE. It was maintained that the work had not been supported by either the Southwood Working Party or the Tyrrell Committee and would not lead to new policy initiatives. The proposal was not put forward for funding by MAFF.

12. During 1993, **(YB 93/10.07/5.1-5.16)** Dr MacOwan bid for MAFF funds in the Blue Book for £40,000 in the 1994/1995 financial year to invest in scrapie to cattle transmission experiments. Only a small sum was bid because of SEAC's previously expressed view that this research should not be pursued and because it was the view of the policy customer that the research would be of academic interest only.

13. On 14 October, 1993 **(YB 93/10.14/9.1)** the CVL's BSE Programme Management Group (PMG) sent a concept note, written by Mr G Wells and Dr Kimberlin to Mr K C Taylor, Mr Eddy, Dr D Matthews, Mr I B Robertson, Mr Bradley and Dr MacOwan. The concept note set out the case for research into the response of cattle to infection with natural sheep scrapie, by parenteral inoculation and by feeding calves with scrapie infected brain.

14. On 1 February, 1994 **(YB 94/2.01/4.1-4.7)** Mr R Bradley wrote to the PMG suggesting that they meet to consider four possible areas/objectives for action on BSE infection in sheep in the light of a concept note commissioned from him by the Chief Scientist's Group. Following their meeting to discuss these issues, on 7 February,

1994 **(YB 94/2.07/2.1-2.6)** the PMG responded to Mr Bradley commenting on the issues raised by Mr Bradley. The PMG also indicated that they were producing a proposal to investigate the policy concern that the BSE agent might be endemic in the sheep population. As part of this proposal, they intended to challenge groups of cattle orally with pools of brains from sheep of specific genotype.

15. In 1994, Dr MacOwan bid for MAFF funds in the Blue Book for a further £500,000 for 1995/96 to undertake research to inoculate scrapie into cattle **(YB 94/5.27/8.1-8.8)**.

16. Dr MacOwan wrote to Mr Bradley on 9 February, 1994 stating that inoculating cattle with scrapie would not give information on BSE in sheep unless the source of the inoculum came from sheep likely to be infected with BSE alone, in the absence of scrapie **(YB 94/02.09/4.1-4.2)**. However, Dr MacOwan wrote again to Mr Bradley on 15 February, 1994 indicating that the PMG may have based their proposal on epidemiological data on scrapie **(YB 94/02.15/5.1)**. Dr MacOwan stated that for this reason he could no longer be so sure of his view expressed in his minute of 9 February, 1994 and suggested a meeting between himself, Mr K Taylor, Mr Eddy, Mr Bradley, Mr Wilesmith, Mr Wells, Mr Dawson, Mr Harkness and Dr Kimberlin.

17. On 24 March, 1994 Dr MacOwan sent a minute to Mr Wilesmith and Dr Matthews commenting on the ROAME proposal they had submitted **(YB 94/03.24/11.1-11.2)**. Dr MacOwan indicated he strongly supported the genotyping of natural scrapie cases and that this should have a high priority given that the potential of the technique was now clear from Dr Bruce's research. Dr MacOwan raised some queries on the proposals. A meeting was to take place on 19 April, 1994 to discuss the proposal.

18. In his BSE and scrapie research focus document of 26 March, 1994 **(YB 94/3.26/1.1)** Mr Bradley maintained that studies in the USA have challenged cattle orally with field scrapie isolates. He stated that all of these cattle were still clinically healthy two and a half years post challenge. Mr Bradley identified a number of difficulties in the proposed study.

19. Prior to the meeting on 19 April, 1994, on 12 April, 1994 Mr Wilesmith sent an updated draft of the ROAME proposal to Mr Meldrum, Mr Haddon, Mr K Taylor, Mr Eddy, Dr MacOwan, Mr Bradley, Mr Dawson, Mr Wells, Mr Harkness, Mr Jackman and Dr Kimberlin **(YB 94/04.12/5.1-5.17)**. The proposal was further amended following comments made at the meeting on 19th April, 1994.

20. In April, 1994 **(J/ID/169/814)** a paper was published in the Journal of Infectious Diseases detailing further work carried out at the USDA on the transmission of scrapie to cattle. In this study, 18 new-born calves were challenged intracerebrally with pooled scrapie infected sheep brain. Half of the calves were euthanased one year

post inoculation. All calves kept longer than one year developed clinical symptoms of a spongiform encephalopathy. The brain of each calf was examined for lesions and PrP^{Sc}. The lesions were found to be subtle but PrP^{Sc} was found in all calves challenged with the scrapie inoculum. The disease characteristics were found to be different from those of BSE. This paper is attached to Mr Bradley's minute of 3 May, 1994 **(YB 94/05.03/9.1-9.9)**.

21. As agreed at the meeting on 19 April, 1994 the ROAME proposal was subdivided into two separate ROAME proposals, one to investigate the origin of BSE, the other to determine whether BSE had become endemic in the British sheep population. These were sent on 12 May, 1994 [**YB 94/5.12/1.1-1.2**] to the Chief Veterinary Officer, Mr Haddon, Mr K Taylor, Mr T Eddy, Dr D Matthews, Mr R Bradley, Mr Harkness, Mr Wells, Mr Dawson, Mr Jackman, Dr Kimberlin, Dr K MacOwan and Dr K Brown.

22. On 16 May, 1994 Mr Bradley sent a minute to Mr K Taylor, Mr Eddy, Dr MacOwan and Dr Matthews **(YB 94/05.16/6.1-6.2)**. Mr Bradley referred to a discussion he had had with Dr Foster from the NPU. Mr Bradley stated that it was evident that the agent derived from the brain of positive line sheep challenged with the same pool of BSE as negative line sheep was quite unlike BSE. Mr Bradley commented that the "scrapie to cows" project should take account of the NPU findings.

23. In his minute of 17 May, 1994 **(YB 94/5.17/3.1-3.2)** to those who had received the PMG proposals, Dr MacOwan supported the ROAMEs provided their titles were changed to "Studies to establish the pathology of endemic scrapie to cattle" and "Studies to identify scrapie strains with short incubation periods in mice" respectively.

24. On 1 June, 1994 **(YB 94/6.01/6.1-6.2)** Dr MacOwan wrote to those who were to attend the meeting on 2 June, 1994 to outline his views on the proposals. He restated that both of the proposals were acceptable to him if their titles were changed although he considered the proposal to challenge cattle orally with scrapie to be of high risk as it was unlikely to show that BSE was in the British sheep population.

25. On 7 June, 1994 Dr MacOwan received a copy of Mr Matthews minute of 18 May, 1994 commenting on the ROAME proposals discussed at the meeting on 2 June, 1994 **(YB 94/05.18/7.1-7.4)**.

26. The following experiments are currently on-going in this particular area:

SE1919: Studies to identify possible homologies between scrapie agents in the British sheep population and the agent of BSE by strain typing in mice

This project is being funded by MAFF at the VLA. It began in April 1995 and is due to be completed in March 2003.

Samples from over 400 sheep clinically affected with scrapie will be collected, confirmed histopathologically and genotyped. Originally it was agreed that two brain homogenates would be prepared: one would be from sheep genetically susceptible to BSE but resistant to scrapie; the other would be from sheep genetically susceptible to scrapie. These were going to be strain typed in a panel of mice. The protocol was going to be repeated for over 400 sheep in which clinical signs developed after April 1998 in order to detect cases of BSE infection that may be characterised by long incubation periods.

However this project has subsequently been extensively discussed at the meeting of the SEAC sheep sub-group on 30 September 1998. It was decided by the sub-group that a selection of the brains collected early in the study should be individually strain-typed in short panels of mice. Taking this study and the IAH study (SE1423) together, a total of 60 individual brains will strain typed. This number was decided by considering the statistical probabilities of detecting BSE in sheep. Accordingly brains from one sheep per genotype per farm are being selected for individual strain typing.

Results are not yet due.

SE0213: An epidemiological study of sheep scrapie to determine means of natural transmission

This study is funded by MAFF at the VLA. It began in April 1995 and is due to be completed in March 2002.

7,000 breeding ewes from 14 flocks will be monitored for incidence of clinical scrapie to provide estimates of annual age-specific incidence. The effect of genotype on the risk of developing clinical scrapie and whether it is a confounder of parental infection status will be determined. Where scrapie occurs in sheep of scrapie resistant genotype, samples are being taken and the strain present is being determined by bioassay in a panel of mice in project SE1938 at the VLA.

A preliminary finding has been that genetic susceptibility to scrapie may vary between flocks as well as between breeds. This may be due to the strain of scrapie present within the flock, implying that a sheep with a genotype resistant to one strain of scrapie may not be resistant to different strains.

SE1423: Transmission studies for the detection of BSE in sheep

This study is being funded by MAFF at the IAH Neuropathogenesis Unit. Research started in April 1996 and is due to be completed in March 2001.

Brain samples were collected from sheep clinically affected by TSE and genotyped. Samples from animals with BSE susceptible but scrapie resistant genotypes will be inoculated into a panel of mice. Samples from animals that have scrapie susceptible genotypes will also be inoculated into a panel of mice for controls. The incubation

periods and lesion profiles will be recorded from the mouse panels and compared with similar previous studies.

No results have been obtained to date.

Experimental challenge of cattle with scrapie

After extensive discussions and consideration of the American research results, a research proposal for work on the pathogenesis of scrapie in cattle and to investigate the effect of rendering procedures on the scrapie agent was submitted to the Chief Scientist's Group in September 1996. This proposal was split into two separate proposals at the request of the Chief Scientist's Group and these were submitted in July 1997. In the interim, the arrangements to provide accommodation for the experimental cattle were put in place.

SE1942: The attack rate and phenotype of scrapie-like disease on transmission to cattle of fresh and rendered pools of scrapie

This study is being funded by MAFF at the VLA. It began in April 1997 and is due to be completed in March 2006.

Calves have been challenged orally with two different materials; a pool of sheep brain infected with natural scrapie that was collected in 1993, and the same pool after it had been rendered in a process simulating the production of MBM. Groups of 10 calves received an oral dose of 100g, 10g and 1g of one of these pools. The infectivity present in both sets of challenge material is being determined by titration in mice.

Clinical signs in the cattle will be noted and they will be killed on development of clinical disease. The strain of TSE present will be characterised by determining the pattern of lesion profiles in the brains of the cattle and by bioassay of CNS in a panel of mice.

The cattle challenged orally with 100g of scrapie brain remain clinically normal 12 months after challenge.

SE1941: Studies to examine the pathogenicity and phenotype of endemic scrapie in cattle

This study is being funded by MAFF at the VLA. It began in April 1998 and is due to be completed in March 2009.

Cattle will be challenged with homogenate derived from the brains of sheep infected with natural scrapie. This project has two parts:

i) Two separate pools will be prepared of scrapie sheep brains sourced before and during the BSE epidemic (pre- and post-1980). The strains present will be determined by bioassay in a panel of mice. These will be used to inoculate two groups of 10

calves by the intracerebral route, as there is insufficient historical tissues for an oral challenge. Five control cattle will be inoculated with saline.

ii) A pathogenesis study will be performed using oral challenge with scrapie infected sheep brain collected after 1 January 1991, i.e. after the major risk period of sheep to BSE contaminated food. Two pools will be formed according to the PrP genotype of the sheep: $Valine_{136}/Glutamine_{171}$ (high scrapie risk) and $Alanine_{136}/Glutamine_{171}$ (high BSE risk). These pools will be used to separately challenge two groups of 20 calves with an oral dose of 100g. Five calves will be killed at three time points after challenge: 10, 18 and 24 months and at termination (clinical onset or 7 years) and selected tissues will be bioassayed in mice. Ten unchallenged calves will act as controls.

Separate groups of five goats will be inoculated intracerebrally with one of the four pools above in order to verify scrapie infectivity. For both parts, any clinical signs in the cattle will be noted and they will be killed on development of clinical disease. The strain of TSE present will be characterised by determining the pattern of lesion profiles in the brains of the cattle and by bioassay of tissue from their brains in a panel of mice.

It is planned to perform a control challenge of calves with scrapie free sheep brain derived from New Zealand sheep.