



STATEMENT ON SUSCEPTIBILITY OF DIFFERENT GENOTYPES IN SHEEP TO EXPERIMENTAL BSE

This statement represents the opinion of a specialist sub-group of SEAC which met on 11th December 2002 to consider this specific issue. The statement was ratified by SEAC on February 11th.

Background

1. In 1999, SEAC endorsed a recommendation from the SEAC Sheep Subgroup that a long-term control and eradication plan for TSEs in sheep should be established. The National Scrapie Plan (NSP) was initiated on the basis of this recommendation.
2. The rationale of the NSP is to reduce progressively the prevalence of scrapie infection and therefore the incidence of scrapie disease, with an aim to eventually eliminate the disease from the national sheep flock. This is to be achieved by a targeted breeding programme in which levels of resistance to TSEs in sheep are increased according to defined genotypic criteria. Over a number of years the NSP will ensure that the proportion of TSE-resistance genes increases throughout the (highly stratified) sheep flock.
3. Scrapie has been an endemic disease in UK sheep for more than 200 years. Although, there is no evidence that scrapie is a human pathogen, there is still scientific uncertainty about a possible risk to human health from TSE's in sheep. This arises from the possibility that some sheep may have become infected with the BSE agent through the consumption of BSE-contaminated meat and bone meal (MBM). In experimental studies it has been shown that BSE can be transmitted to sheep by the oral route. The inclusion rate of MBM in feed for sheep was much lower than for cattle and, generally, exposure of sheep to contaminated MBM would have been much less than for cattle. Most exposure

would have been prior to the ruminant feed ban of July 1988.¹ However, had BSE been introduced into the sheep population it might have been maintained by transmission from sheep-to-sheep, like scrapie. Also, it may not have been recognised as the clinical signs of experimental BSE in sheep appear to be the same as those of scrapie.

4. The studies conducted to date, including studies of strain-typing of scrapie cases, do not provide evidence that BSE is present in the sheep population. However as a theoretical risk remains, a dual aim of the NSP is to protect against the theoretical risk of BSE through inclusion of the BSE-resistant genotypes in the breeding programmes for scrapie resistance.
5. Susceptibility to natural infection with scrapie and to experimental infection with BSE varies according to the genotype and possibly the breed of the sheep. The underlying principle of the NSP is the premise that the ARR allele confers resistance to TSE's. Previously, this Sub-group has recommended that if new research emerges which indicates that sheep genotypes originally considered to be resistant to scrapie and BSE (e.g. ARR/ARR) were able to incubate disease, the National Scrapie Plan should be reviewed.

Research Findings

6. The views of the SEAC Sheep Sub-group were sought on unpublished results from an ongoing study at the Institute for Animal Health in the UK. This study is funded by Defra. The study was to determine the susceptibility of TSE-free sheep from New Zealand. Sheep of different genotypes were challenged with either BSE or scrapie. Challenge was by intracerebral inoculation for BSE and subcutaneously for scrapie, which are considered to be the most efficient means of transmitting these agents.
7. The new research reports the experimental transmission of BSE to ARR/ARR sheep following intracerebral challenge with 0.5ml 10% BSE-infected bovine brain homogenate. The incubation period of disease is approximately twice the average incubation period of 556 days reported in BSE susceptible genotypes (ARQ/ARQ sheep) challenged by intracerebral inoculation with BSE in the same study. Apart from a single unconfirmed report of

¹ on inclusion of ruminant derived MBM in concentrate foodstuffs for ruminants (the feed ban).

naturally occurring scrapie in Japan, this is the first record of a TSE infection in ARR/ARR sheep.

8. Ongoing studies have indicated that sheep with the genotype ARR/ARR are not susceptible to challenge with BSE, by the oral route. Members noted that to date there have been no cases of TSE- related disease in an ongoing study in which 20 ARR/ARR sheep have been orally dosed with 5g of BSE infected bovine brain homogenate. In this study, groups of 5 sheep (including one unchallenged control) were culled at set time points (10, 22, 34, and 46 months post oral challenge). Using immunohistochemistry, PrP^{Sc} has not been detected in any tissue tested from any of the scheduled culls. A final group of 5 sheep (including one unchallenged control) is being maintained to determine whether these animals will ever succumb to BSE. To date, these animals are now 5 years post challenge and have not developed clinical signs of BSE.
9. In the same study, 20 ARQ/ARR were also orally dosed with 5g of BSE infected bovine brain homogenate. Groups of 5 sheep (including one unchallenged control) were culled at the same time points, with a final group maintained to determine whether these animals will eventually succumb to BSE. As with the ARR/ARR sheep, these sheep remain healthy at 5 years post oral challenge, and PrP^{Sc} has not been detected from any of the tissues tested from the scheduled culls. In contrast, PrP^{Sc} and infectivity was detected in a wide range of tissues from a group of 20 ARQ/ARQ sheep orally dosed with 5g of BSE infected brain homogenate, and all the sheep succumbed to BSE infection between 1.7 and 3.1 years.

Conclusions

10. Members of the Subgroup were asked to consider if this finding had implications for the susceptibility of ARR/ARR sheep to TSEs by natural routes of exposure.
11. Members agreed that the transmission of BSE following intracerebral inoculation shows that the resistance of ARR/ARR sheep to TSE infection cannot be regarded as absolute. They noted, however, that intracerebral inoculation is not a natural route of transmission and had BSE been introduced into the sheep population the most likely route of exposure was oral. Members agreed that, although the new findings did not establish

that BSE could be transmitted to ARR/ARR sheep by natural routes of infection, the possibility could not be excluded.

12. Members noted that ARR/ARR sheep appeared to be highly resistant to infection with scrapie by natural routes, as judged by the absence of cases of scrapie in such sheep. It was noted that very few ARR/ARR sheep had been challenged in experimental studies by intracerebral inoculation of scrapie and their susceptibility to such challenge was unknown. Members also noted that a high proportion of sheep with scrapie susceptible genotypes had developed BSE following experimental oral challenge, confirming the relative resistance of sheep with the ARR/ARR genotype to TSE agents in general.
13. Members acknowledged there were possible parallels with work on experimental TSE's in pigs. In these experiments, transmission of BSE infection had occurred after BSE-infected material had been inoculated intracerebrally combined with other routes. However infection was not established when pigs were fed orally with BSE-infected material. Members agreed, however, that it would be unwise to give undue weight to this parallel observation in interpreting the significance of the new findings in sheep.
14. Members agreed that these new research findings in sheep did not alter the validity of the basic strategy of reducing the prevalence of genotypes susceptible to TSEs as part of the animal and human health case for reducing the prevalence of TSE infections in sheep.

Assessment of the scientific implications for the National Scrapie Plan

15. The scientific rationale for the NSP is to reduce and eliminate the prevalence of any TSE's in sheep. The eradication plan is based on selective breeding to eliminate susceptible genotypes while increasing the prevalence of resistant genotypes (ARR/ARR) in the national flock. Therefore, the general principle underlying the NSP is the premise that the ARR allele confers resistance to TSE's.
16. Members agreed this new research shows that although ARR/ARR sheep are not completely resistant to BSE infection, this genotype is relatively more resistant than other genotypes

examined in the NSP. This is evident from the on-going work with orally BSE challenged ARR/ARR sheep.

17. They concluded that although this research shows that ARR/ARR may not be fully resistant to infection, increasing resistant alleles in the national flock would reduce the potential sources of infection and thus reduce the incidence of clinical disease. This would have the ultimate effect of reducing the possibility of potential human exposure to BSE infectivity via the food chain. Members agreed this latest research is a significant development but they did not consider that the new research undermined the scientific basis of the NSP.
18. Members reiterated previous opinion that the issue of carrier states remains a key uncertainty with regard to scientific justification for the NSP. The theoretical possibility remains that ARR homozygous sheep could act as sub-clinical carriers of TSE infection, capable of maintaining and transmitting infection. If resistant sheep proved to be latent carriers of infection then this may impede elimination of TSE infections via the current breeding strategy. Members acknowledged that the new findings do not directly inform this issue, although they noted that research was in progress to address this. Members suggested that consideration be given to testing tissues from any ARR/ARR sheep surviving at the end of the study for evidence of sub-clinical BSE infection. Members agreed this important scientific issue needs to be kept under constant review to ensure the success of the NSP.
19. Members recommended that continued research was required to understand the biological basis of the genotypic differences in susceptibility to TSE infection.
20. Members noted there were insufficient data on other routes of challenge for TSE's to allow comparison with, or to aid interpretation of, experimental studies on scrapie and on BSE. They recommended that additional experiments be conducted to investigate different routes of challenge for both scrapie and BSE (i.e. peripheral routes of exposure for BSE and ic challenge for scrapie).