



## **Summary of results from on-going research studying experimental BSE in sheep**

### Background

1. Although naturally occurring BSE has never been detected in sheep, sheep were fed the same contaminated feed which is believed to have caused BSE in cattle, albeit in smaller quantities. Therefore there exists the possibility that BSE may be present in the sheep population. In addition, BSE can be successfully transmitted experimentally to sheep thereby indicating their susceptibility to BSE.
2. Defra funds a number of research projects to investigate:
  - How BSE would present in sheep and how this would differ from scrapie
  - If BSE can be transmitted vertically or horizontally
  - If BSE is present in the sheep population today, after several passages through sheep, would it still appear to be BSE-like or would the characteristics of the disease be altered so it now appeared scrapie-like.
3. Most of this research is still on-going and the full results will not be available for a number of years. However this paper will outline main results emerging from this research. For details of experimental methods, interim results, and incubation periods, please see attached Annex<sup>1</sup>.

### Susceptibility of Genotypes

4. Sheep have been challenged either orally or intracerebrally (ic) with BSE. Both routes of challenging sheep have clearly shown that sheep with genotype ARQ/ARQ are the most susceptible. ARQ/ARQ sheep will succumb to disease approximately 628-1132 days after being orally challenged with BSE and 495-671 days following ic challenge.

However information on the other genotypes is less clear. To date no other genotype has succumbed to oral challenge with BSE, including ARQ/ARR sheep, and most of the information has come from ic challenge of animals. However ic inoculation of sheep is a very artificial route of challenging sheep and makes it difficult to interpret the significance of the findings. Table 1 below summarises the results to date

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<sup>1</sup> *Annex of this paper is has not been circulated outside the committee as the annexe contain new scientific data that have not yet been published in a scientific or medical journal. As premature release of unpublished data may prejudice publication the annexe are not released prior to publication. This is in accordance with SEAC's code of practice*

Table 1: Incubation periods of sheep challenged with BSE

<b>Genotype</b>	<b>Incubation period (days) Ic</b>	<b>Incubation period (days) Oral</b>
ARQ/ARQ	495-671	628-1132
ARQ/ARR	o/g	o/g
ARR/ARR*	1008-1127	o/g
VRQ/ARR	o/g	n/a
VRQ/ARQ*	912-1008	n/a
VRQ/VRQ*	1046-1060	n/a

\*The ic challenge of these genotypes is still on-going and the incubation periods are based on small numbers of animals

o/g = on-going research where animals remain alive 5.5 years post challenge

n/a = not available; genotypes have not been challenged orally

- The table clearly shows that the ic route of challenge causes disease in a wider range of genotypes and most significantly in ARR/ARR sheep. Results recently presented to the SEAC sheep sub-group described the disease in 3/19 ARR/ARR at 1008-1127 days following ic challenge with cattle BSE. This is nearly twice as long as the average incubation in ARQ/ARQ sheep at of 524 days post inoculation (pi). The SEAC sub-group concluded that whilst this result was scientifically interesting, it does not affect the premise of the National Scrapie Plan.

#### Analysis of Tissue/sheep pathogenesis

- The oral route of challenging sheep with BSE is most likely to represent how the disease could have been introduced into the sheep population. Therefore to investigate how infectivity would spread through a sheep orally challenged with BSE the VLA have challenged sheep orally with BSE and culled the animals at set intervals post infection (SE1929). This work has found that PrP<sup>Sc</sup> can be detected in a number of tissues from as early as 4 months post challenge in ARQ/ARQ sheep. Table 2 shows when infectivity can be detected in tissues either by immunohistochemistry (IHC) or mouse bioassay. This project has also challenged ARQ/ARR and ARR/ARR orally with BSE. However analysis of tissues from these animals have failed to detect PrP<sup>Sc</sup> up to 48 months post challenge and the remaining sheep are healthy up to 5.5 years post challenge.

Table 2: List of tissues shown to be positive for PrP<sup>Sc</sup> following oral challenge with BSE

<b>Tissue*</b>	<b>PrP<sup>Sc</sup> Detected (months pi)</b>
Peyer's patches	4
Retropharyngeal lymph node	4
Spleen	10

Mesenteric lymph node	16
Prescapular lymph node	16
Thymus	16
Sub-mandibular lymph node	16
Tonsil	16
Brain	16
Spinal cord	16

\*Full results are available in the summary of SE1929

### Minimum Oral Dose and Sub-passage of BSE

7. As stated above, if BSE has been introduced into the sheep population through the same contaminated feed that the cattle were exposed to. However the sheep would have received the contaminated feed in far smaller quantities than cattle. Therefore Defra are funding research to investigate what the minimum oral of BSE that is required to cause disease in sheep. In this experiment sheep have been orally dosed with 5g, 0.5g, 0.05g, 0.005g or 0.0005g of BSE. The results from this work will help inform models assessing the risk of sheep having been exposed to enough contaminated feed to have caused BSE.
8. It is well known that scrapie has been present in the sheep population for at least 200 years and has been maintained most likely by vertical transmission. Therefore it is possible that if BSE is present in the sheep population it could be maintained in a similar way to scrapie. To investigate what BSE in sheep may appear like today sheep have been challenged with BSE isolated from sheep challenged with cattle BSE. Initial results appear to indicate that the secondary passage of BSE in sheep gives Western blot results that are still BSE-like. One experiment has also just started to investigate the tertiary passage of sheep BSE.
9. To investigate the possibility of vertical (maternal) transmission, sheep have been challenged with BSE before mating with rams of known genotypes to ensure that susceptible offspring are born. So far there has been no sign of disease in any of the offspring, some of which are now 7 years old.
10. Horizontal transmission is also a possibility so to investigate this susceptible sheep have been mixed with sheep challenged with BSE. However this work has only just started and there are no results to date.

Defra  
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