

## **Recent Developments from Defra's TSE Research Unit**

### **Issue**

Members will be presented with an update on the Defra TSE Research Programme (2001 to 2002).

### **Advice Sought from the Committee**

None. This paper is provided for information only.

### **1. General Points**

Since the emergence of BSE in 1986, Government has spent over £140m on TSE research. Research is funded principally by Defra, DH, FSA, BBSRC and MRC. Currently, the spend on TSE research by these bodies totals around £30m per annum, of which Defra contributes around £16.6m.

#### *1.1. Research Budget*

Following the Defra Comprehensive Spending Review (CSR) settlement, the Department now has a fixed ceiling on the TSE research budget. This is fully committed for 2002/3 and 2003/4 which leaves little flexibility for the inclusion of new work.

	<b>Proposed Research spend (£)</b>		
	<b>Baselines</b>		
<b>ROAME Programme</b>	<b>2003/04</b>	<b>2004/05</b>	<b>2005/06</b>
BSE in cattle	2,482	2,527	1,378
Diagnostics	2,668	1,514	1,500
TSEs in sheep	10,986	11,845	10,164
By Products	494	668	556
Risk analysis/ reviews/ workshops	49	45	40
<b>Total</b>	<b>16,679</b>	<b>16,599</b>	<b>13,638</b>

## *1.2. Science and Innovation Strategy*

In line with the recommendations of the Defra Chief Scientific Advisor, a Departmental TSE Science and Innovation Strategy Document has been drafted. This is a statement of the Department's research needs to support the evidence base for policy actions on TSEs. This is expected to be made public by May this year.

## *1.3. UK Strategy for Research and Development Relating to the Human and Animal Health Aspects of Transmissible Spongiform Encephalopathies*

The TSE research and development strategy in the UK was previously presented in two documents:

- Strategy for research and development relating to human health aspects of TSEs (published in November 1996 by DH with MAFF, BBSRC and MRC input)
- Strategy for research and development relating to animal health aspects of TSEs (published in July 1998 by MAFF and DH with input from BBSRC).

In view of the growing overlap of science and the improved co-ordination of TSE research in the UK, the UK funders of TSE research and development are in the process of drafting a new strategy document. The strategy will be released for public consultation during May and June 2003 and is due for publication in September 2003.

## **2. BSE – General**

### *2.1. Key Research*

Defra is continuing to support key applied research to maintain policies that are in line with the new Departmental objectives and PSA targets. In particular we will be continuing to fund the epidemiology studies that will model and determine projections for the progress of the disease in cattle. There will be particular focus on the monitoring and analysis of information on the BARB group of animals that have been born since the rigid enforcement of feed controls in 1996.

## **BSE – Specific**

### *2.2. Minimum Oral Dose*

Information on the minimal oral dose required for transmission of BSE to cattle is important for supporting risk modelling and epidemiology studies of BSE. Such studies are also important as they provide information on the appearance of disease in cattle that have been exposed to a range of doses. Similar sheep experiments are also on-going investigating minimum oral dose for sheep experimentally infected with BSE.

On-going Defra funded studies are examining the disease transmission to cattle orally challenged with low single doses (0.001g, 0.01g and 0.1g) of BSE.

### *2.3. Maternal Transmission*

John Wilesmith, VLA, has recently informed us of further modelling work performed on the data in the BSE surveillance database to investigate the level of maternal associated risk. These studies indicate that the cumulative maternal risk, based on the whole GB epidemic data, is now reduced to 2%, but with a confidence interval including zero.

### *2.4. Distribution of BSE Infectivity*

Defra has supported extensive work to investigate the distribution of BSE infectivity in cattle tissues. The testing of tissues in mice has been underway since the early 1990's. Present work is examining the distribution of BSE infectivity in disease time-point tissues of cattle orally challenged with BSE. This work is now funded by the FSA.

The current study involves intra-cerebral inoculation of tissues into recipient cattle to eliminate species barrier effects with mice. A recent result has documented disease transmission to 1 recipient bovine challenged with a pooled tonsil sample, collected from cattle 10 months post oral challenge.

### *2.5. Tests to Monitor MBM for Ruminant Protein to be Evaluated by the EU*

The development of diagnostic tools to test for the adulteration of compound animal feed with mammalian meat and bone meal or other banned animal material, continues to be a Defra priority. The

development of these tests will build on existing tests and represents the primary control point for preventing future BSE transmission to cattle.

Defra has several test development projects on-going and one research and development project has recently been completed. This is based on a molecular based DNA amplification method and is claimed to satisfy EC test sensitivity requirements. It is envisaged that further validation of this test will be required before it can be adopted for routine use.

The EU is establishing a ring-trial to evaluate tests currently available for monitoring compound animal feedstuff compliance to legislation. The Veterinary Laboratories Agency has formally been nominated to represent the UK's interests in this trial.

### *2.6. BSE Strain Stability*

Histological results from a recently completed Defra funded project have indicated that BSE in cattle has remained uniform throughout the course of the BSE epidemic. This provides some evidence that a single agent was responsible for the cause of BSE and subsequently has remained stable throughout the epidemic.

## **3. Diagnostic – General**

### *3.1. Joint Funders Open Competition*

The development of tests suitable for pre-clinical detection of TSE disease in animals as well as those capable of differentiating between prion “strains” has remained a priority for Defra.

A Joint Funders initiative for the development of diagnostic tests for TSEs has resulted in Defra funding 10 new research projects in the diagnostics area.

### *3.2. Pre-clinical Diagnostic Test*

A major objective of TSE research has been the development of one or more tests that may be used to identify TSE infection in live animals before clinical signs are apparent. This is especially important with these diseases because of their long incubation periods during which they may pose a risk to animal health or public health.

Some progress has been made with the development of the I.C.E. (immunocapillary electrophoresis test) test at the VLA. The method has been shown to identify positive sheep from scrapie flocks at certain stages of infection before clinical disease develops. Further work is being done to determine the exact age range in which positive animals can be identified. Scrapie-free animals give negative results with the test. The method therefore shows promise as a diagnostic tool but its use on a wide scale will be determined by the final characteristics of the test, in particular the optimum time for the test to be used to identify TSE positive sheep. The preparatory stages for samples in this test are relatively complex and require several days to process; this may limit the number of samples that can be processed and the scale of use of the test. Currently the I.C.E. method remains the only non-invasive live animal test that has the development potential for identifying TSE-infected sheep

### *3.3. Call for Research Using Spectroscopic Methods*

Recently, Defra has been involved with the FSA and BBSRC in holding a workshop on the application of spectroscopic methods for TSE disease diagnosis and particularly for the differentiation of BSE and scrapie. As a result of this workshop, a call for research proposal was advertised at the end of last year with a closing date for applications on 24 January 2003.<sup>1</sup>

The application of spectroscopic techniques, including mass spectrometry may enable the structure of the prion protein to be investigated and hence these methods may be useful for TSE strain differentiation. Spectroscopic strain differentiation methods would compliment on-going Defra funded work developing methods to differentiate BSE and scrapie in sheep.

## **4. Diagnostic – Specific**

### *4.1. Recent University of California (San Francisco) publication*

Stanley Prusiner and colleagues has recently published data partly as a result of Defra funded work. This publication states to have developed extremely sensitive immunological and transgenic mouse bioassay methods for BSE diagnosis.

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<sup>1</sup> <http://www.defra.gov.uk/research/RRD/CTX0203.pdf>

#### *4.2. Differential diagnostic test – EC ring trial*

The VLA in its capacity as a European Reference Laboratory has been commissioned to draw up the strategy for investigating the possible presence of BSE in the sheep population. As part of this requirement, the VLA will be conducting a ring-trial evaluation of existing rapid molecular-based methods for differential diagnosis. As well as methods developed by the VLA and two French groups, Professor John Collinge of the MRC Prion Unit and Dr Jiri Safar (California) have been asked to put their methods forward for this trial. The test developed by Dr Safar was, in part, funded by Defra.

#### *4.3. Second EC ring trial to evaluate five rapid tests for the diagnosis of TSEs in bovines*

Five new rapid molecular tests for clinical disease diagnosis of BSE in cattle are currently being evaluated in an EC ring trial. These tests will complement the existing 3 EC approved tests. The report of phase 1 of this ring trial was published on 27 March 2002.<sup>2</sup> Further validation of these tests on a large number of BSE positive and negative brain samples, and in a number of laboratories, is still on-going.

### **5. TSEs in Sheep – General**

#### *5.1. Current Research*

The work funded in this area is generally in support of the National Scrapie Plan (NSP) and policies in support of public health. The Unit will continue to fund research in support of this high priority area.

#### *5.2. Impact of NSP on Production Traits*

There is a possibility that the NSP may impact on certain production traits in sheep and that this may inhibit farmers from joining the NSP. Defra is not currently funding research in this area which is becoming increasingly important. Although we have received two related proposals, currently out to peer review, which would allow us to perform research into the impact of the NSP on production traits, our current financial constraints may prevent these projects from being funded.

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<sup>2</sup>Available on the Institute for Reference Materials and Measurements website  
[http://www.irmm.jrc.be/bse\\_1.pdf](http://www.irmm.jrc.be/bse_1.pdf)

### *5.3. Impact of NSP on the Biodiversity of Rare Breeds*

Defra is committed to maintaining the biodiversity of species in this country. However the Rare Breed Survival Trust (RBST) considers that the NSP will limit the genetic resources needed for the survival of a number of the breeds. Defra are currently working with the RBST and it is hoped that a research proposal will be established to look at ways to enable the NSP to proceed with the minimum impact on rare breeds. It is envisaged that this project will be funded from the NSP budget but would be managed by the TSE Research Unit.

### *5.4. Detecting Differences Between Scrapie and BSE*

Investigating possible difference between scrapie and BSE in sheep continues to be a high priority. To achieve this several approaches are being investigated, in particular rapid molecular tests exploiting recent developments in technology.

### *5.5. Carrier State*

An area where there is increasing interest is investigating the possibility of a carrier state in resistant sheep. Defra currently funds a number of projects in this area. This work involves analysing tissues from ARR/ARR sheep which have been challenged with either scrapie (oral challenge) or BSE (oral and intra-cerebral challenge) for signs of infectivity. These tissues are being analysed by Western blot, mouse bioassay and immunohistochemistry.

## **6. TSEs in Sheep – Specific**

### *6.1. Recent ARR/ARR Result*

Defra, in collaboration with the Institute for Animal Health, recently reported that a New Zealand sheep of ARR/ARR genotype had succumbed to intracerebral challenge with BSE. As ARR selection is the basis of the NSP this result has now been discussed by the SEAC Sheep Subgroup who concluded that although the new finding did not establish that BSE could be transmitted to ARR/ARR sheep by natural routes of infection, the possibility could not be excluded. (See item 3 of the agenda for the SEAC 77 meeting).

## 7. Other Developments

### 7.1. Environment Workshop

To complement Defra's existing research a workshop was held in April 2002 to identify research priorities in the area of TSE's in the environment.<sup>3</sup> A number of research questions were identified including the development of better prion or TSE infectivity detection methods for application to the environment. Unfortunately, constraints in Defra's Research and Development budget has not enabled work in this area to be funded.

### 7.2. Current Research

Defra is currently funding two research proposals in this area.

- The first is investigating whether susceptible TSE free New Zealand (NZ) sheep succumb to scrapie after being exposed contaminated environments. This will be achieved in a number of ways including lambing both NZ sheep and natural exposed scrapie sheep together, housing NZ sheep in lambing sheds after the scrapie sheep have been removed and exposing the NZ sheep to contaminated pastures. Following exposure the NZ sheep are removed to a scrapie free facility and monitored for signs of disease.
- Defra has also commissioned a study to investigate the persistence and movement of BSE in open soil experiments. This study has important implications for risks of environmental transmission and contamination of ground waters. The study may also provide important information to support assumptions used in risk assessments (e.g. the hydrophobic nature of the prion protein). Despite the importance of this project, the progress of this work has been affected by delays in the project.

### 7.3. Independent Archive Advisory Group

The Veterinary Laboratories Agency holds approximately 60,000 tissues from TSE affected animals in its TSE Tissue Archive for distribution to researchers world-wide who would not otherwise have access to TSE infected material. It is a limited resource which requires an effective management strategy to ensure the distribution of tissues to researchers is fair, transparent and appropriate. An Independent Archive Advisory Group (IAAG) has

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<sup>3</sup> A report of the Workshop can be found on Defra's Website ([http://www.defra.gov.uk/science/Publications/TSE\\_WORKSHOP\\_30\\_04\\_2002.pdf](http://www.defra.gov.uk/science/Publications/TSE_WORKSHOP_30_04_2002.pdf))

therefore been established to set the policy for release of tissues and assess individual requests for tissues where the tissue is rare or the request is unusually complex. The group is chaired by Professor Sir Peter Lachmann from the University of Cambridge and is comprised of five independent experts and representatives from the European Commission, Defra and other Government Departments.

The establishment of this group was recommended by the *Review of Defra Research 1995–2000* ('the McConnell Review').