



SCIENTIFIC BASIS FOR CLASSICAL SCRAPIE CONTROLS

ISSUE

1. The Department of Environment Food and Rural Affairs (Defra) has asked for advice on the potential risks to human health in relation to changes to control measures implemented when transmissible spongiform encephalopathy (TSE) infections are found in sheep flocks.

BACKGROUND

2. Regulation (EC) No.999/2001 (the TSE Regulation) came into force in July 2001, laying down rules for the prevention, control and eradication of certain TSEs. In 2004, Regulation (EC) No.1492/2004 amended the TSE Regulation to require Member States to implement compulsory controls on sheep flocks and goat herds affected with scrapie. Following identification of any TSE in a sheep flock, the whole sheep flock, or those sheep in the flock of genotypes more susceptible to classical scrapie, had to be destroyed instead of slaughtered for human consumption. The latter option allowed sheep carrying at least one ARR allele to be slaughtered for human consumption. For goat herds, whole herd culling was the only option.
3. At SEAC 89 (September 2005) Defra and the FSA sought advice from SEAC on the European Union's TSE Roadmap, which was published in July 2005. The TSE Roadmap sought to ensure that any relaxation of TSE controls would be science-based and would not endanger either public health or the policy of eradicating BSE. The TSE Roadmap proposed a relaxation of the culling policy for all cases of TSE in small ruminants where BSE was excluded on the basis of the availability of new diagnostic tools which could discriminate BSE from scrapie. SEAC welcomed the TSE Roadmap and made the following comments in relation to proposals for relaxing the culling policy for small ruminants:

"Members noted that culling could partly be driven by surveillance, but because of the widespread distribution of infectivity in small ruminants, culling could also be a consumer

protection measure. One key consideration in the assessment of future culling policy appeared to be how often in the past other cases of the disease had been identified in the same flock through culling. It was noted that whole flock culling may adversely affect the reporting of cases. The committee commented that, if maternal or intra-flock transmission was found to be significant in sheep, this might impact on an assessment of culling as a risk reduction measure.”¹

4. In 2006, the European Commission commenced discussions with Member States on legislation to relax the culling requirements as proposed in the TSE Roadmap.
5. The French Government objected to changes that would allow animals from sheep flocks known to be affected by classical scrapie to enter the human food chain, on testing negative for TSEs using an approved rapid test, on the grounds that this may present a significant risk to human health. The objection was based on an evaluation of the implications of the changes by the French Food Safety Agency (AFSSA)² (see later and Annex 1).
6. Aware of the AFSSA opinion, the Commission asked the European Food Safety Authority (EFSA) to consider the key issues identified by AFSSA. After considering the resultant opinion produced by the EFSA Scientific Panel on Biological Hazards³ (see later and Annex 2), the Commission, following a majority vote by Member States, introduced changes to the controls, including the option to allow sheep from flocks where a classical scrapie infection has been identified to be slaughtered for human consumption, without any restriction on the genotype of the animals, on testing negative for a TSE infection using approved rapid tests. The UK supported the proposal.
7. Regulation (EC) No.727/2007 came into force in July 2007 amending the TSE Regulation. The changes were numerous and complex. Broadly, they provided Member States with some latitude in the application of measures to control the infection in

¹ Minutes of SEAC 89 on 25th September 2005 paragraphs 17-18. <http://www.seac.gov.uk/minutes/final89.pdf>

² Opinion of the French Food Safety Agency (AFSSA) given on 15th January 2007 on changes to the control measures for sheep and goat herds in which a case of classical or atypical scrapie has been detected. <http://www.afssa.fr/Documents/ESST2006sa0343EN.pdf>

³ Opinion of the Scientific Panel on Biological Hazards given on 8th March 2007 on certain aspects related to the risk of transmissible spongiform encephalopathies (TSEs) in ovine and caprine animals http://www.efsa.eu.int/EFSA/Scientific_Opinion/biohaz_op_ej466_tse_ovine_caprine_summary_en.pdf

sheep flocks or goat herds known to be affected by TSE. The changes permitted Member States to allow sheep from flocks where a TSE had been identified, that had been determined not to be BSE by discriminatory molecular testing of the index case, to be slaughtered for human consumption (rather than being killed and destroyed), provided that animals aged over 18 months first tested negative for TSE.

8. The French Government subsequently applied to the European Court of First Instance to annul the clauses in Regulation (EC) No.727/2007 that allowed animals from flocks known to be affected by classical scrapie to be slaughtered for human consumption (rather than being killed and destroyed). In September 2007, the Court of First Instance, suspended these clauses as an interim measure, pending a full hearing. The interim decision made by the Court which provides the reasoning behind that decision is at Annex 3 for background information.
9. The German Government has also sought advice from its scientific advisory committee on TSEs (KOM AG TSE) on the changes to the controls. This committee expressed concern about the human health implications of allowing animals from flocks known to be affected by classical scrapie to be slaughtered for human consumption following a negative result on TSE testing⁴ (see Annex 4 and later).
10. Defra has asked SEAC to consider the opinions of AFSSA, EFSA BioHazard Panel and KOM AG TSE, to review previous advice given by SEAC, and to provide advice on the possible human health risks in relation to the changes to the classical scrapie controls that allow animals from flocks known to be affected by classical scrapie to enter the human food chain.
11. The advice from SEAC will inform Defra considerations on how to respond to the action taken by the Court of First Instance and could form part of a submission to the Court by the UK.
12. This paper summarises the key conclusions of AFSSA, the EFSA BioHazard Panel and KOM AG TSE in relation to the allowing animals from flocks known to be affected by classical scrapie to be slaughtered for human consumption following a negative result on TSE testing of animals aged over 18 months of age. Previous views expressed by SEAC relevant to this issue are also provided

⁴ No reference available.

as well as a summary of a recent estimation of the prevalence of BSE in sheep by EFSA.

AFSSA OPINION

13. The AFSSA opinion (Annex 1) describes three areas of scientific uncertainty that have led to the conclusion that the proposed changes to controls may significantly increase the risk to human health from the slaughter of sheep from classical scrapie affected flocks for human consumption. In summary, AFSSA considered that:

- the tests to detect and discriminate between BSE and classical and atypical scrapie are limited as (i) their sensitivity has not been accurately determined, (ii) they may not detect BSE in animals that are also infected with classical scrapie and (iii) the conduct of the discriminatory test on the index case would not guarantee the absence of BSE in the flock. Furthermore, as only brain tissue is tested, the rapid tests cannot detect TSE infections during the incubation period prior to accumulation of abnormal prion protein in the brain.
- although there are no epidemiological data to suggest a link between classical scrapie strains and human TSEs, in view of the diversity of classical scrapie strains and the lack of a robust prospective study to examine potential links between these TSE strains and human TSEs, a link cannot be ruled out.
- the incidence of classical scrapie infections in classical scrapie affected sheep flocks can be relatively high, particularly in those animals of susceptible genotypes⁵ suggesting classical scrapie infection may be widespread in affected flocks.

14. In view of these considerations, AFSSA concluded that allowing animals from classical scrapie affected flocks to be slaughtered for human consumption, particularly without any restriction on genotype, would increase the human health risk as:

(i) the presence of BSE in a sheep cannot be ruled out by the application of discriminatory tests as the sensitivity of the tests is

⁵ Corbiere *et al.* (2007) Advanced survival models for risk-factor analysis in scrapie. *J. Gen Virol.* 88, 696-705.

not known precisely and detection may be compromised when classical scrapie is also present.

(ii) classical scrapie infections can be widespread in sheep flocks and as rapid TSE tests cannot identify infected animals in the early part of the incubation period, it is possible that an appreciable number of classical scrapie infected animals could enter the human food chain.

(iii) the transmission to humans of TSE strains other than BSE cannot be ruled out.

EFSA OPINION

15. The EFSA Scientific Panel on Biological Hazards considered the AFSSA opinion and in particular the evidence for possible links between classical or atypical scrapie and human TSEs and the performance characteristics of discriminatory tests for sheep TSEs (Annex 2). The Panel concluded that:

- there is no evidence for an epidemiological or molecular link between classical and/or atypical scrapie and TSEs in humans. The BSE agent is the only agent identified as zoonotic. However, in view of their diversity it is currently not possible to exclude transmissibility to humans of other animal TSE agents.
- current discriminatory tests appear, up to now, to be reliable for the differentiation of BSE from classical and atypical scrapie. However, at the current stage of scientific knowledge, neither their diagnostic sensitivity nor their specificity can be assumed to be perfect.

KOM AG TSE OPINION

16. KOM AG TSE considered the changes to classical scrapie controls (Annex 4) and noted that recently published research by Reckzeh *et al.* (2007)⁶ (Annex 4) showed that some sheep of susceptible genotypes that had tested negative for TSE infection when brain samples were tested, were in fact positive for TSE infection when peripheral tissues were tested. Thus, the committee concluded that the current strategy of testing brain tissue cannot exclude the presence of TSE infections at the stage of the incubation period prior to involvement of the brain. Thus, the changes to classical

⁶ Reckzeh *et al.* (2007) Rapid testing leads to the underestimation of the scrapie prevalence in an affected sheep and goat flock. *Vet. Microbiol.* 123, 320-327.

scrapie controls could allow classical scrapie infectivity into the human food chain.

17. In addition, the committee noted that, although the EFSA Biohazard Panel concluded that there are no indications of the existence of zoonotic link between classical scrapie and human TSEs, as classical scrapie strains are not uniform and are poorly defined, a zoonotic potential cannot be ruled out. In view of this, the committee considered that consumer exposure to classical scrapie should be avoided and was not in favour of the changes to the classical scrapie controls that would allow this to occur.

PREVIOUS SEAC OPINIONS

18. Taken together the three opinions above describe three key areas of scientific uncertainty that influence the assessments of the human health risks in relation to permitting animals from known classical scrapie affected sheep flocks to be slaughtered for human consumption:

(i) whether the application of the discriminatory test to the index case would reliably enable the presence of BSE to be excluded either in the tested animal (with the potential confounding factor of possible presence of mixed classical scrapie-BSE infections masking the presence of BSE) or the flock to which it belongs given the possible co-existence of different TSE strains in the same flock.

(ii) the possibility that classical scrapie may be transmissible to humans cannot be ruled out, although there is an absence of evidence for such a link.

(iii) that rapid tests are not capable of detecting infections at early the stage of the incubation prior to accumulation of abnormal prion protein in the brain.

19. The SEAC Sheep Subgroup has provided views relevant to some of these issues. Extracts from SEAC Sheep Subgroup statements are provided below.

Discriminatory tests for sheep TSEs

20. The SEAC Sheep Subgroup has not specifically evaluated the performance of the discriminatory tests for sheep TSEs in detail. However, in considering the issue of differentiating classical and

“...robust diagnostic methods are now available to differentiate between classical scrapie, atypical scrapie and experimental BSE in sheep, lowering the likelihood of classical scrapie masking the presence of BSE in sheep.”⁷

BSE in sheep

21. The SEAC Sheep Subgroup has considered the possibility of BSE in the national sheep flock on a number of occasions. Most recently, the Subgroup considered this issue as part of a review of the National Scrapie Plan in 2006. The Subgroup concluded that:

“...sheep are likely to have been exposed historically to MBM in feedstuffs, although at levels far below those to which cattle were exposed, probably less than 3% of the cattle exposure. Furthermore, BSE has been shown to be transmissible to sheep, experimentally, by the oral route^{8,9}. Thus, it is not unlikely that, historically, sheep in the UK flock were infected with BSE. There is evidence for BSE in a French goat which had been fed MBM, and a UK goat has been identified with probable BSE which may also have been acquired through feed. However, as described below, there is no evidence that BSE is currently present in the UK flock. Thus, if BSE ever entered the UK flock it is most likely to have been at a level that would not lead to a self-sustaining epidemic once feeding MBM to ruminants was banned in 1988.

Relatively recently, the Veterinary Laboratories Agency (VLA) developed a validated, discriminatory hybrid immunoblotting method which can distinguish between experimental BSE in sheep, classical scrapie and atypical scrapie^{10,11}. It has only ever been applied to experimental BSE in sheep as there are no examples of natural BSE infection. However, there is no reason to believe that

⁷ SEAC Sheep Subgroup statement (2006) <http://www.seac.gov.uk/statements/sheepsubgrp-statement131006.pdf>

⁸ Foster *et al.* (2001) Distribution of the prion protein in sheep terminally affected with BSE following experimental oral transmission. *J. Gen. Virol.* 82, 2319-2326

⁹ Bellworthy *et al.* (2005) Tissue distribution of bovine spongiform encephalopathy infectivity in Romney sheep up to the onset of clinical disease after oral challenge. *Vet. Rec.* 156, 197-202

¹⁰ Stack *et al.* (2002) Differentiation of prion protein glycoforms from naturally occurring sheep scrapie, sheep-passaged scrapie strains (CH1641 and SSBP1), bovine spongiform encephalopathy (BSE) cases and Romney and Cheviot breed sheep experimentally inoculated with BSE using two monoclonal antibodies. *Acta neuropathol. (Berl)* 104:279-86

¹¹ Stack M. *et al.* (2006) Monitoring for bovine spongiform encephalopathy in sheep in Great Britain, 1998-2004. *J. Gen. Virol.* 87, 2099-107

natural and experimental BSE infections should behave differently in this assay. This discriminatory technique has been applied retrospectively to all scrapie positive cases identified by passive surveillance in GB between 1st January 1998 and 31st October 2001, with prospective testing of both passive and active surveillance samples from November 2001 onwards. No case of BSE in UK sheep has been found.

Based on the 2483 TSE positive samples tested from 605 flocks, statistical calculations¹² indicate that the most likely proportion of TSE-positive cases in sheep that could potentially be BSE is zero, with an upper 95% confidence limit of 0.49% of TSE positive cases in sheep that could potentially be BSE. On a yearly basis, combining the maximum proportion of sheep TSE cases that could be BSE with the number of flocks which are TSE affected (established from the scrapie notifications database¹³), gives for year 2002 a maximum of eight flocks (95% CI: 5-10) which could be affected by BSE, most of which will have only a single case, and a maximum of six flocks (95% CI: 4-8) and seven flocks (95% CI: 5-10) for years 2003 and 2004, respectively. During this period, there was a total of around 70 000 flocks in the UK.

Another modelling study¹⁴, based on a different approach but using similar estimates for the most likely proportion of TSE positive cases in sheep that could potentially be BSE, combined with data from the 2002 scrapie postal survey, also concluded that the most likely number of BSE cases in the UK sheep flock was zero and that, in the worst case, no more than four flocks might currently harbour an ongoing BSE epidemic.

...the most likely prevalence of BSE in the UK sheep flock is zero, and in the worst case no more than ten flocks would be infected. As MBM is banned in ruminant feed, if BSE was present it would be likely to spread very slowly. Maternal transmission alone is unlikely to be sufficient to sustain a BSE epidemic in the national sheep flock¹⁵. However, a recent study has shown that natural transmission of BSE between sheep in an experimental flock can occur¹⁶. It is, therefore, critical that an effective surveillance regime

¹² Data provided by Simon Gubbins

¹³ Data provided by Victor del Rio Vilas

¹⁴ Fryer *et al.* (2007) Quantifying the risk from ovine BSE and the impact of control strategies. *Proc. Biol. Sci.* 274, 1497-1503.

¹⁵ Foster *et al.* (2004) Maternal transmission studies of BSE in sheep. *J. Gen. Virol.* 85, 3159-3163.

¹⁶ Bellworthy *et al.* (2005) Natural transmission of BSE between sheep within an experimental flock. *Vet. Rec.* 157, 206

remains in place to provide early identification of an emerging BSE epidemic, should it ever occur in the future.

Assuming that maternal transmission of BSE on its own would not be sufficient to sustain an epidemic, if it is indeed present in the national flock, its prevalence would reduce over time. In addition, given the feed controls introduced in the UK and throughout the EU, and the declining BSE epidemic in cattle, the likelihood of BSE entering the national flock through a food borne source is now very small. In 2001 methods had not been sufficiently well developed to allow routine surveillance to distinguish between BSE and classical scrapie, and thus the possibility that there were many BSE cases in the UK flock could not be discounted. Now that it is possible to distinguish BSE from classical scrapie the evidence shows that there are at most few BSE cases in sheep and the most likely number is zero.”¹⁷

EFSA opinion on the prevalence of BSE in sheep

22. In 2007, an analysis by EFSA estimated the prevalence of BSE in sheep in the European Union based on data from TSE surveillance of sheep slaughtered for human consumption. It was estimated with 95% confidence that there are between zero (the most likely prevalence) and, depending on assumptions made about the sensitivity of discriminatory testing, two to four BSE infections per 10 000 sheep in the UK. Similarly, and depending on the model and input surveillance data, there is a 95% confidence that in the high risk subgroup of countries (UK, France, Ireland and Portugal) there are fewer than 0.3-0.5 cases of BSE per 10 000 healthy-slaughter animals¹⁷.

Mixed BSE and classical scrapie infections

23. The SEAC Sheep Subgroup also considered in 2006 the possibility of mixed infections of classical scrapie and BSE and how they may influence understanding of the prevalence of BSE in sheep:

“...in the situation of mixed infections of BSE and classical scrapie the outcome is at present uncertain. Unpublished data from transmissions to mice of mixtures of BSE and classical scrapie reportedly indicate that scrapie like properties are detected in these transmissions, which would suggest that classical scrapie may

¹⁷ EFSA (2007) Opinion of the Scientific Panel on Biological Hazards on a request from the European Commission on the quantitative risk assessment on the residual BSE risk in sheep meat and meat products. *The EFSA Journal* 442, 1-44.
[http://www.efsa.europa.eu/EFSA/Scientific Opinion/biohaz_op_ej442_qra_sheep_en.3.pdf](http://www.efsa.europa.eu/EFSA/Scientific%20Opinion/biohaz_op_ej442_qra_sheep_en.3.pdf)

mask the presence of BSE. However the Sheep Subgroup has not yet seen these data and so cannot comment on their reliability or otherwise. It would be important to determine the properties of mixed infections and clarify the discriminatory power of the various tests in such situations. However, as experimental BSE infection can occur in non scrapie infected sheep, and as the number of classical scrapie infected sheep is very low (0.33% of the national flock¹⁸), the chances of a mixed infection are extremely low.”⁷

Link between classical scrapie and human TSEs

24. The SEAC Sheep Subgroup noted a lack of evidence for an association between classical scrapie and human TSEs:

in 1999, “Scrapie has been an endemic disease in UK sheep for more than 200 years without any apparent association with human disease. Nevertheless, there is still uncertainty about a possible risk to humans from sheep TSEs, mainly because of the possibility that BSE may have transmitted to sheep prior to the feed ban.”¹⁹

in 2006, “...reducing the incidence of classical scrapie per se would not directly reduce the risk to public health the risk to public health, since classical scrapie has been evident for over 200 years and there is no evidence it poses a significant risk to human health.”⁷

DISCUSSION

25. The differing estimates of the possible prevalence of BSE in the UK sheep flock, based on discriminatory testing, and assuming the tests are reliable for the differentiation of classical and atypical scrapie and BSE, suggest that the prevalence of BSE in UK sheep is zero (the most likely prevalence) or low, if present at all. Given this low or zero prevalence, the principal risks associated with permitting animals from flocks known to be affected by classical scrapie to be slaughtered for human consumption following a negative result on TSE testing, appear to be (i) the potential for animals infected with early stage classical scrapie (or mixed classical scrapie-BSE infections), where the infection is restricted to peripheral tissues (not categorised as specified risk material) to enter the human food chain; and (ii) for that exposure to result in human disease.

¹⁸ Defra surveillance report

<http://www.defra.gov.uk/animalh/bse/publications/reports/SheepSurveyRpt.pdf>

¹⁹ SEAC (1999) SEAC subgroup report research and surveillance for TSEs in sheep. <http://www.seac.gov.uk/publicats/sub-rep.pdf>

26. In light of the evidence that a proportion of classical scrapie infections in animals in the earlier stages of the incubation period are not detected by testing brain samples, it is possible that a proportion of infected animals from sheep flocks known to be affected by classical scrapie enter the food chain, depending on how wide spread the classical scrapie infection is in the flock. However, as only a small proportion (approximately 2% in the UK) of sheep aged over 18 months, slaughtered for human consumption are currently tested for the presence of a TSE, it is not clear what proportion of sheep entering the food chain are carrying subclinical classical scrapie infection and how the level of classical scrapie infectivity entering the food chain might be affected if the culling requirement was removed.
27. The evidence suggesting a lack of a link between classical scrapie and human TSEs is limited to:
- observations that classical scrapie has been an endemic disease in sheep for more than 200 years without any apparent association with human disease.¹⁹
 - observations that sporadic Creutzfeldt-Jakob Disease (sCJD) exists in countries such as Australia and New Zealand with no reported cases of classical scrapie (despite limited active surveillance).
 - a case-control study and an epidemiological report examining risk factors for sCJD^{20,21} (provided at Annex 5).

ADVICE SOUGHT FROM THE COMMITTEE

28. The committee is requested to:
- consider and comment on the scientific opinions expressed by AFSSA, the EFSA BioHazard Panel and KOM AG TSE, in particular on the zoonotic risk of classical scrapie and the reliability of discriminatory tests.
 - advise on the potential human health risk in relation to allowing animals from known classical scrapie affected flocks to be slaughtered for human consumption provided a negative result is obtained on TSE testing animals over 18 months of age.
 - produce a statement.

²⁰ Brown *et al.* (1987) The epidemiology of Creutzfeldt-Jakob disease. Conclusion of a 15-year investigation in France and review of the world literature. *Neurology*. 37, 895.

²¹ van Duijn *et al.* (1998) Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. *Lancet*. 351, 1081-1085.



Opinion of the French Food Safety Agency (AFSSA) on changes to the control measures for sheep and goat herds in which a case of classical or atypical scrapie has been detected

<http://www.afssa.fr/Documents/ESST2006sa0343EN.pdf>



Opinion of the Scientific Panel on Biological Hazards on certain aspects related to the risk of transmissible spongiform encephalopathies (TSEs) in ovine and caprine animals

http://www.efsa.europa.eu/EFSA/Scientific_Opinion/biohaz_op_ej466_tse_ovine_caprine_en.pdf



Interim Order by the European Court of Justice



Opinion of the KOM AG TSE

Evaluation of the catalogue of measures after detecting a TSE case

Reckzeh *et al.* (2007) Rapid testing leads to the underestimation of the scrapie prevalence in an affected sheep and goat flock. *Vet. Microbiol.* 123, 320-327.



Brown *et al.* (1987) The epidemiology of Creutzfeldt-Jakob disease. Conclusion of a 15-year investigation in France and review of the world literature. *Neurology*. 37, 895.

van Duijn *et al.* (1998) Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. *Lancet*. 351, 1081-1085.