# SEAC SHEEP SUBGROUP REPORT

## ISSUE

1. To consider the SEAC Sheep Subgroup statement on the science underpinning the Ram Genotyping Scheme (RGS) and Welsh Ewe Genotyping Scheme (WEGS).

## BACKGROUND

2. The SEAC Sheep Subgroup met on 13th October 2006 to consider the science underpinning the RGS and WEGS. The statement from the meeting has been agreed by Subgroup members and is provided to SEAC members (Annex 1).

## ADVICE SOUGHT FROM THE COMMITTEE

3. The committee is invited to comment on and endorse the Sheep Subgroup statement.

**DRAFT**

# SEAC SHEEP SUBGROUP STATEMENT

## Issue

1. Defra, together with the Devolved Administrations (DAs) and the Department of Agriculture and Rural Development, Northern Ireland (DARDNI), and in consultation with the Food Standards Agency (FSA), is reviewing the National Scrapie Plan (NSP) and Northern Ireland Scrapie Plan (NISP) voluntary Ram Genotyping Schemes (RGS)[1]. As part of that process, SEAC was asked for its views on the latest science underpinning the breeding programme. The SEAC Chair agreed the Sheep Subgroup should undertake this work on behalf of SEAC and provide a report for SEAC.

2. The Welsh Assembly Government's Minister for Environment, Planning and Countryside gave his agreement to a review in 2006 of the Welsh Ewe Genotyping Scheme (WEGS). The Welsh Assembly Government (WAG) similarly asked for SEAC's views on the latest science underpinning the current scheme and on proposed modelling studies.

## Introduction

3. The NSP RGS was launched in July 2001 as a voluntary long term breeding programme for purebred flocks, based on a review of the scientific evidence available at that time[2]. The aims of the NSP are two-fold: to protect animal health by reducing, and eventually eradicating, scrapie; and to protect public health from the theoretical risk of BSE if it is present in sheep and is masked by scrapie. Thus, the aim is to reduce the proportion of sheep with a PrP genotype genetically susceptible to classical scrapie and replace these with sheep of genotypes more resistant to classical

[1] The advice sought from SEAC was for both the NSP and NISP breeding programmes. However, for ease, the rest of this statement deals only with the NSP's RGS as it operates in Great Britain, although NISP's RGS operates under the same rules and restrictions.
[2] SEAC sheep subgroup report (1999):Research and surveillance for TSEs in sheep. http://www.seac.gov.uk/publicats/sub-rep.pdf

scrapie over time. A voluntary breeding programme, similar to the NSP RGS, was introduced in Northern Ireland in 2003.

4. In 2001, in parallel with the launch of the NSP RGS, the WEGS was funded by the WAG. A successor scheme, WEGS II, was aimed at genotype replacement of ewe lambs in pure-bred flocks at the top of the breeding pyramid, which when mated with scrapie resistant rams identified through the RGS, would produce progeny of increased scrapie resistance.

5. More recently[3], the European Parliament agreed in principle that it should be optional, not compulsory, for Member States to operate genotype based breeding programmes. In the light of this, Defra and DA Ministers agreed that the future of the NSP's existing voluntary RGS should be reviewed.

6. The RGS has, as intended, resulted in significant changes to the PrP genotype profile of many sheep breeds. Genotyping of rams and ram lambs has been undertaken in the majority of ram breeding flocks with genotype frequencies moving significantly towards those which will reduce the risk of classical scrapie. It was predicted[4], at the outset, that the proportion of lambs in the slaughter lamb population that have at least one ARR allele, but no VRQ allele, would rise from 69% in 2002 to 76% by 2007, given 100% uptake of the RGS. More recent estimates[5] suggest that the increase predicted has been achieved. The Sheep Subgroup accepted evidence that the changes in allele frequency have been essentially those predicted at the outset of the scheme, and that therefore the scheme has been very effectively implemented.

7. At the time of their launches, both the RGS and WEGS were appropriate policies given the underpinning scientific evidence available. However, SEAC advised from the outset that the relevant scientific data were limited and that, therefore, the scientific basis for the NSP and the RGS should be kept under review to take account of emerging scientific evidence.

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[3] Article 6 a of Regulation (EC) No 999/2001. European Parliament tabled legislative report 27 April 2006 p.17
Reports of the European Parliament
With subsequent legislative opinion 17 May 2006 p.14
Texts adopted by Parliament

[4] Roden J.A., Nieuhof G. and Bishop S. (2002) Modelling selection strategies to increase genetic resistance to scrapie in the national flock of Great Britain-phase 1. unpublished data.

[5] Roden J.A. and Gubbins S. unpublished data

8. Such a review is now timely. Since 2001, there have been a number of significant scientific advances which potentially impact upon the rationale for the NSP. First, rapid sensitive diagnostic tests have enabled large scale surveillance leading to the identification of a new group of atypical scrapies. Second, robust diagnostic methods are now able 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. Third, despite extensive use of these techniques in surveillance, BSE has not been detected in sheep in the UK. Fourth, atypical scrapie has been detected in the UK and a number of other EU Member States. In most cases this was a subclinical infection detected by active surveillance. Atypical scrapie is now best considered as caused by a TSE agent distinct from those responsible for BSE and classical scrapie[6]. Fifth, atypical scrapie has been identified in sheep with genotypes most resistant to classical scrapie and experimental BSE in sheep. In addition, the implementation of the ban of meat and bone meal (MBM) in ruminant animal feed has been very effective in reducing the risk of BSE entering and spreading through the national sheep flock.

## Advice sought from the Sheep Subgroup regarding the RGS

9. The Sheep Subgroup was asked for its views on:-

- whether the risk from BSE in sheep can be quantified, and if so what degree of risk reduction is afforded by the RGS
- whether concerns over atypical scrapie alter the scientific basis for the RGS
- whether removing VRQ only is a valid approach to controlling classical scrapie, given that scrapie also occurs in other genotypes such as ARQ.

The Sheep Subgroup considered scientific developments addressing the following questions, posed by Defra, the DAs and DARDNI in consultation with the FSA:

### BSE in Sheep

*If BSE entered the national sheep flock from historic exposure to contaminated feed and can be naturally transmitted between sheep, what is the probability that it would have been found by now, given the level of surveillance?*

[6] http://www.seac.gov.uk/pdf/positionstatement-sheep-subgroup.pdf

10. The Sheep Subgroup noted that sheep are likely to have been historically exposed to MBM in feedstuffs, although at levels estimated to be 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[7,8]. 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.

11. 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[9,10]. 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 natural and experimental BSE infections should behave differently in this assay.

12. 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 sheep has been found.

13. Based on the 2483 TSE positive samples tested from 605 flocks, statistical calculations[11] indicate that the most likely proportion of

[7] Foster J.D., Parnham D.W., Hunter N. and Bruce M. (2001) Distribution of the prion protein in sheep terminally affected with BSE following experimental oral transmission. *J. Gen. Virol*. **82**, 2319-2326

[8] Bellworthy S.J., Hawkins S.A.C., Green R.B., Blamire I., Dexter G., Dexter I., Lockey R., Jeffrey M., Ryder S., Berthelin-Baker C. and Simmons M.M. (2005) Tissue distribution of bovine spongiform enceophalopathy infectivity in Romney sheep up to the onset of clinical disease after oral challenge. *Vet. Rec.* **156**, 197-202

[9] Stack M.J., Chaplin M.J. and Clark J. (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

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

[11] Data provided by Simon Gubbins

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 number of sheep TSE cases that could be BSE with the proportion of flocks which are TSE affected established from the fallen stock survey, gives a maximum of 17 flocks which could be affected by BSE, most of which will have only a single case, for year 2002 and a maximum of seven flocks for year 2005. There is a total of around 70 000 flocks in the UK.

14. Another modelling study[12], 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 (see paragraph 22).

15. The Sheep Subgroup concluded that the most likely prevalence of BSE in the UK sheep flock is zero, and in the worst case no more than 17 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 flock[13]. However, a recent study has shown that natural transmission of BSE between sheep in an experimental flock can occur[14]. It is, therefore, critical that an effective surveillance regime remains in place to provide early identification of an emerging BSE epidemic, should it ever occur in the future.

*If the uncertainty in the possible prevalence of BSE in sheep is too large, what additional research and/or surveillance would be required to make a more accurate determination of the likelihood of BSE being present in the national sheep flock?*

16. The Sheep Subgroup concluded that the only way to be certain that BSE is not in the UK flock is to screen every sheep and this is clearly not practical or sensible. The current surveillance regime will, over a long period, reduce the confidence limits of the

[12] Fryer H.R., Baylis M., Sivam K., McLean A.R. prepublication data

[13] Foster J.D., Goldmann W., McKenzie C., Smith A., Parnham D.W. and Hunter N. (2004) Maternal transmission studies of BSE in sheep. *J. Gen. Virol*. **85**, 3159-3163

[14] Bellworthy S.J., Dexter, G., Stack M., Chaplin M., Hawkins S.A.C. and Simmons M.M. (2005) Natural transmission of BSE between sheep within an experimental flock. *Vet. Rec*. **157**, 206

estimates further. However, increased surveillance would provide diminishing returns and, unless surveillance was very substantially increased, would not substantially reduce the confidence limits. The estimate of prevalence of BSE in sheep could also be further refined by taking genotype susceptibility to BSE into account, given that experimental transmissions have shown that ARQ/ARQ genotypes are more susceptible to BSE than ARR/ARR genotypes.

17. Surveillance is dependent on a rapid test identifying a TSE infection and discriminatory tests distinguishing BSE from other sheep TSEs. The final confirmatory discriminatory test for BSE involves bioassay in a panel of different mouse strains. Unpublished data from transmissions to mice of mixtures of BSE and classical scrapie reportedly indicate that scrapie like properties are detected in these transmissions. This suggests that classical scrapie may mask the presence of BSE, calling into question the ability of the mouse bioassay to detect BSE in the presence of classical scrapie. If this result is confirmed it would be important to clarify the discriminatory power of the various tests when applied to mixed classical scrapie and BSE infections. 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 flock[15]), the chances of a mixed infection are extremely low.

18. The Sheep Subgroup emphasised that continued surveillance worldwide remains essential to detect any new or emerging TSE epidemics.

*What is the current likelihood of BSE being present in the UK national sheep flock, and how does it compare with 2001?*

19. 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

[15] Defra surveillance report
http://www.defra.gov.uk/animalh/bse/publications/reports/SheepSurveyRpt.pdf

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 (see paragraph 13).

*Are the numbers of cases of vCJD in line with model predictions if the only source of infection was cattle or is there evidence of an ovine origin? Have vCJD cases from food borne sources stabilised or declined?*

20. There have, up to September 2006, been 162 definite and probable cases of vCJD in the UK[16]. The Sheep Subgroup accepted the data and conclusions on the human vCJD epidemic, presented at SEAC 94[17], that the number of vCJD cases is entirely consistent with infection originating from BSE-infected cattle. Specifically, the peak of the current wave of human cases mirrors the peak of infected cattle entering the human food chain with a delay of approximately eight years. However it was not possible to exclude the possibility that another source of dietary infection was the cause of a small proportion of the clinical vCJD cases. It would only become apparent that there were non-bovine sources of primary infection in the circumstance that a significant number of vCJD cases arise in individuals who could only have been infected after the introduction of the feed and SRM controls for cattle.

21. It was not possible to answer the question of whether vCJD cases from food borne sources had stabilised or declined. The current profile of clinical cases shows a peak in 2000, and a subsequent decline. However, all these individuals are of the MM genotype and further peaks of vCJD cases may well occur, with longer incubation periods, in non-MM individuals still attributable to the original BSE epidemic in cattle. It was noted that there were a number of cases of vCJD worldwide, with no history of UK residence, whose source of infection was not yet elucidated.

*If BSE is present in the national sheep flock, what is the amount of BSE infectivity that might be entering the food chain and from how many sheep? How does this compare with the amount of infectivity that is estimated to have entered the food chain historically due to bovine and/or ovine BSE?*

[16] Monthly CJD statistics : The Department of Health - P&G: Health topics: CJD
[17] SEAC Homepage (NB minutes to be ratified at SEAC 95) presentation by Dr Richard Knight, NCJDSU.

22. The Sheep Subgroup noted that modelling[12] showed that one BSE infected sheep, close to the end of its incubation period, may contribute 10 to 1000 times more infectious material to the food chain than an infected cow. This is because thirty per cent of the risk from a BSE infected sheep is likely to come from infectivity in lymphatic and peripheral tissue that cannot be completely removed from a carcass by removal of SRM under normal abattoir conditions. This modelling indicated that although a maximum of four flocks might currently harbour an ongoing BSE epidemic, the annual human exposure from four flocks could be as much as 0.5% of the total exposure from cattle over the whole BSE epidemic. This is, of course, a worst case scenario. Given that, to date 162 definite and probable vCJD cases have arisen in the UK ascribed to the bovine epidemic, extrapolation suggests that, in the worst case, if BSE were in the UK sheep flock it might add a further 1 to 2 deaths per annum, assuming that these 162 cases represented the total number of people infected through exposure to cattle BSE. The most likely number is, however, zero.

23. From the modelling study[12], small reductions in the risk of food chain exposure from sheep could be achieved by strategies based on tissue testing, a 12 month age restriction or expanded definitions of high risk tissues. However, the most effective risk reduction strategies would remain genotype based.

24. It was also noted that recent unpublished studies suggested that the BSE agent, once passaged through ovine transgenic mice, might become more virulent, transmitting more quickly with faster incubation times and infecting a greater number of species.[18] If this result can be confirmed, extrapolation suggests that ovine BSE may be more infectious to humans than bovine BSE. However, the Subgroup has not seen the primary, unpublished, data and therefore cannot comment on their reliability.

*What reduction in risk to public health is delivered by*
*(i) an aim to produce small year on year increases in the percentage of resistant and semi-resistant animals being eaten?*
*(ii) reduce the incidence of classical scrapie and BSE if present?*

[18] Torres J.M., Espinosa J.C., Andréoletti O., Herva M.E., Alamillo E. and Lacroux C. (2006) BSE agent shows an enhanced virulence after passage in sheep. European network of Excellence Neuoprion Conference Turin. Abstract ORAL-18

25. The Subgroup noted that the RGS was producing changes in the sheep genotype pool.[19] However, as the most likely scenario is that there is currently no BSE in sheep in the food chain, the RGS could, by definition, not reduce the risk from BSE further. In the worst case scenario, discussed above (paragraph 22), BSE infected sheep entering the food chain would provide a relatively small increase in vCJD risk compared with that experienced from the bovine epidemic. Thus, continuation of the RGS and alteration of the sheep genotype pool would make little or no further contribution to reducing the risk to public health from BSE.

26. The Subgroup noted that codon 168 could be significant regarding resistance to BSE infection in sheep[20] but may be restricted to a few breeds. The relevance with regard to the national flock remains to be investigated.

27. The Subgroup concluded that reducing the incidence of classical scrapie *per se* would not directly reduce 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. However, it should not be forgotten that the RGS classical scrapie reduction has significant benefits to farmers and animal welfare. Furthermore, the RGS continues to prove a useful source of information, enabling knowledge to be gathered on the genotype of the national sheep flock. This knowledge will prove useful should, in the future, BSE or indeed a new TSE enter the sheep flock.

28. Elimination of classical scrapie would also have indirect, potential benefits for human health. Although the threat of a BSE epidemic in sheep is now low, as long as surveillance is maintained worldwide the high resistance to BSE in the national flock would present a barrier to subsequent re-introduction of BSE from external sources. Additionally, the origin of BSE is unknown and the possibility it arose from scrapie, although improbable, cannot be excluded. If scrapie were the origin of BSE, removal of classical scrapie from the UK sheep flock would prevent BSE re-emerging. It was also noted that breeding towards arginine at codon 171 of

[19] Warner R.G., Morris D. and Dawson M. (2006) PrP genotype progression in flocks participating in the National Scrapie Plan for Great Britain.*Vet. Rec*. **159,** 473-9

[20] Goldmann W., Houston F., Stewart P., Perucchini M., Foster J. and Hunter N. (2006) Ovine prion protein variant $A^{136}R^{154}L^{168}Q^{171}$ increases resistance to experimental challenge with bovine spongiform encephalopathy agent. *J. Gen. Virol.* **87**, 3741-3745

the PrP gene would reduce the exposure of humans to TSEs from replication of prions in the peripheral tissues of sheep[21] .

**Atypical Scrapie**

*Does the Subgroup agree with the conclusions in the European Food Safety Authority's report on the breeding programme for TSEs in small ruminants[22]?*

29. The Sheep Subgroup was concerned that the wording of some of the statements in the EFSA report and summary could lead to misunderstanding. However, they agreed with the key aspects of the EFSA report, subject to the following specific reservations:

- *Production traits*

30. The Subgroup generally concurred with this conclusion, with the caveat that there may be an association between survival of lambs 1 to14 days old with the ARR/ARR genotype in certain breeds[23], this needs further investigation. Additionally, further work is needed to inform on whether breeding towards ARR/ARR genotypes would alter susceptibility to atypical scrapie (see below).

- *Atypical scrapie*

31. The Subgroup noted that the EU breeding strategy was to take action on the VRQ allele only and it was assumed in the Opinion that the proportion of the ARR allele in the sheep population would increase. However, in a population with a number of different alleles controlling expression of a single trait such as scrapie resistance/susceptibility, the Subgroup agreed that, unless one specific allele such as ARR was actively selected for, the proportion of that allele will not increase dramatically simply by eliminating one unfavourable allele such as VRQ[24] .

[21] Jeffrey M., Begara-McGorum I., Clark S., Martin S., Clark J., Chaplin M and Gonzalez L. (2002) Occurrence and distribution of infection-specific PrP in tissues of clinical scrapie cases and cull sheep from scrapie-affected farms in Shetland. J. Clin. Pathol. 127, 264-273

[22] http://www.efsa.europa.eu/etc/medialib/efsa/science/biohaz/biohaz_opinions/ej382_breeding_sheep.Par.0004.File.dat/biohaz_op_ej382_breeding_sheep_TSE_en.pdf

[23] Information provided by Stephen Bishop

[24] Roden J.A., Nieuwhof G.J., Bishop S.C., Jones D.A., Haresign W. and Gubbins S. (2006) Breeding programmes for TSE resistance in sheep. I. Assessing the impact on prion protein genotype frequencies. *Prev. Vet. Med*. **73**, 1-16

32. The Subgroup considered that the EFSA BioHaz Panel conclusion *"Given the low frequency of multiple cases within flocks and the level of susceptibility of the ARR genotype there is a very low risk of disease in the remaining ARR/ARR animals in a flock that had atypical scrapie. The BioHaz panel therefore recommends continuing the current breeding programme."* is premature. It is clear that genotypes considered resistant to classical scrapie are still susceptible to atypical scrapie and that, therefore, any breeding programme aimed at resistance to classical scrapie will not necessarily breed for resistance to atypical scrapie and could even reduce resistance. Further data acquisition and analysis are required before any conclusion can be drawn regarding whether the current breeding programme to remove the VRQ allele will alter the prevalence of atypical scrapie in the UK flock.

*What studies are needed to inform on whether there is a risk to public health from atypical scrapie? What data would lead the subgroup to consider that atypical scrapie is a greater potential risk to public health than BSE in sheep? How long are such studies likely to take? Can the risks to consumers, if any, from BSE or atypical scrapie in sheep be compared and if so, how?*

33. No studies examining the human health risks of atypical scrapie have been completed. Therefore, such a risk cannot yet be excluded. Current risk reduction measures such as SRM and MBM feeding bans reduce any risk, should it exist. The Subgroup referred to its position statement which contained recommendations for further studies[6]. The Subgroup noted that experiments were under way to assess the transmissibility of atypical scrapie in mice expressing human PrP genotypes. They were encouraged by a recent report[25], although the unpublished data was not presented to the Subgroup, that atypical scrapie was present in sheep samples from 1989, making it less likely that it is a new and rapidly spreading infection or a risk to human health. The Subgroup agreed that studies to assess the risk of atypical scrapie relative to BSE and classical scrapie in mice would take many years, and it needs to be recognised that results from the mouse model alone may not necessarily inform whether or not atypical scrapie is a human health risk.

34. On the transmissibility of atypical scrapie, which may have implications for human health, it was suggested that relevant

[25] Unpublished information from the Institute for Animal Health

departments should consider in advance their responses to results which may emerge.

*If the RGS continues, what are the risks associated with potentially creating a sheep population that is susceptible to atypical scrapie? What are the implications for a) human health and b) animal health?*

35. The Subgroup agreed that the current RGS would likely be less effective in reducing susceptibility to atypical scrapie in the national flock than it is in reducing susceptibility to classical scrapie. It was not yet clear how the RGS would alter susceptibility to atypical scrapie in the national flock, and the present data are so scarce that it is not possible to be certain whether the RGS would increase or decrease prevalence[26]. It was agreed that further work was needed to establish the prevalence of atypical scrapie within the different genotypes and breeds, and modelling of these data could inform on the expected impact of the RGS over the next 5 to 10 years on atypical scrapie prevalence.

36. The Subgroup was informed of preliminary and limited epidemiological data[27] indicating, on the basis of trading associations, that atypical scrapie is unlikely to be spreading quickly. Given a slow spread of disease, the Subgroup considered that, since atypical scrapie cases were present in many European countries, this is consistent with the hypothesis that it is not a new disease but has been present for some considerable time. If atypical scrapie has been present for 200 years, as has classical scrapie, it was considered that the risks to human health would be small. Data collected long term were needed to inform on this aspect. To date, the earliest case of atypical scrapie in GB dates back to 1989[25].

37. The RGS operates on a 3 codon screening system for codons 136, 154 and 171. The Subgroup recommended consideration of the inclusion of codon 141 in any genotyping programme for sheep, to take account of the importance of this allele regarding susceptibility to atypical scrapie[28].

38. There have been six clinical cases of atypical scrapie to October 2006 in the GB flock, but others may have gone undetected. The

[26] Baylis M., Bishop S., Hope J. and Kao R., (2006) Analysis for the SEAC sheep subgroup
[27] Data provided by Rowland Kao
[28] Saunders G.C., Cawthraw S., Mountjoy S.J., Hope J. and Windl O. (2006) PrP genotypes of atypical scrapie cases in Great Britain. *J.Gen. Virol*. **87**, 3141-9

full clinical phenotype is still undefined. It was noted that clinical signs tend to appear in older animals than for classical scrapie. The Subgroup considered the data insufficient to assess the potential impact of atypical scrapie on animal health. Additional research is needed here.

## Classical scrapie

*Is removing only the VRQ allele a valid scientific approach to controlling scrapie given that scrapie occurs in other genotypes, such as ARQ? Alternatively is there scope for a flock by flock approach, dependent on the genotype of the index case and the remainder of the flock?*

39. The Subgroup agreed, given that approximately 70% of classical scrapie cases occur in sheep with the VRQ allele, removing the VRQ allele would lead to a significant reduction in classical scrapie from the current level. It is known, however, that classical scrapie also targets the ARQ allele. In Germany and Cyprus there is a classical scrapie epidemic in ARQ sheep and some breeds in the UK have an extremely low proportion of VRQ/VRQ genotypes such that ARQ is the main classical scrapie susceptible allele. Although removing VRQ would lead to a considerable reduction in infectivity levels, there would still be the potential for persistent infection with current or emerging TSE strains in ARQ sheep.

40. Regarding a flock by flock approach, the Subgroup was informed of a modelling study by Gubbins[29] which indicated that simply removing animals with clinical signs, could, over decades, result in classical scrapie ultimately disappearing from the national flock, but not in all circumstances. Using this information, a modelling study by Gubbins and Webb[30] indicated that the most effective strategy, measured in terms of the probability of eradication and time taken for eradication, was predicted to be whole flock culling, which was effective under all the scenarios they considered for the long term dynamics of scrapie. Strategies involving whole flock genotyping with selective culling were also effective, though they were predicted to take longer to eradicate scrapie than whole flock culling. Ram genotyping schemes were effective in some instances, but not for the scenario where scrapie remained endemic in the national flock.

[29] Gubbins S. (2005) A modelling framework to describe the spread of scrapie between sheep flocks in Great Britain. *Prev. Vet. Med.* **67**, 143-156

[30] Gubbins S. and Webb C.R. (2005) Simulation of the options for a national control programme to eradicate scrapie from Great Britain. *Prev. Vet. Med*. **69**, 175-187

41. The Subgroup agreed that all schemes depended on a ready supply of classical scrapie resistant rams for breeding, once culling of classical scrapie suspects had been carried out. Some form of genotyping strategy, compulsory or voluntary, could ensure this supply.

42. The Subgroup agreed that further information is needed on strains of classical scrapie in different genotypes to determine whether a flock by flock approach would be useful. Atypical scrapie would also have to be taken into account and culling decisions based on the index case could be difficult.

**General questions**

*Which is the most appropriate way, based upon science, to control classical scrapie/BSE in sheep – breeding for resistance or targeted culling?*

43. The Subgroup agreed that a combination of targeted culling and subsequent breeding for resistance would be most effective. However, it was recognised that this would have to be tailored to each affected flock depending on whether the index case was BSE, classical scrapie or atypical scrapie, taking into account the genotype composition and movements of sheep. A ready supply of sheep of appropriate resistant genotype would be needed to repopulate the flock.

*Is there still a scientific basis for continuing with the RGS to a) protect public health and b) protect animal health?*

44. From modelling studies[24] removing only VRQ alleles, as in the current RGS, has very little impact on the frequency of the ARQ allele in the slaughter lamb population, the allele associated with the highest risk of BSE in sheep. Given this, and the fact that the prevalence of BSE in the sheep population is likely to be very low, the Subgroup concluded that the current RGS would have little impact on human health, with the following caveats. First, as discussed in paragraph 17, there is a suggestion, although it has not yet been possible to assess the unpublished primary data, that mixed infections of BSE and classical scrapie might mask BSE. Further work is needed to clarify this point. However, as it is known the two TSEs can exist independently, and each is present at low frequency in the national flock, the number of mixed infections will

be extremely low. Secondly, the current RGS could alter the prevalence of atypical scrapie (see paragraph 35). Given the unknown human health risk from atypical scrapie, the extent to which the current RGS would alter the human health risk is uncertain. In the relatively unlikely event that atypical scrapie does pose a risk to human health, the impact of the current RGS on human health risks would need to be quantified.

45. Ultimately, an appropriate genotyping programme, and if necessary a breeding programme, will ensure a balance of alleles is maintained which keeps the incidence of TSEs low, prevent a reservoir of infection and inform later studies. A genetically uniform population could be highly susceptible to a new TSE, should it arise.

46. The Subgroup consider the current RGS is still scientifically valid with respect to animal health to protect against classical scrapie with the caveat that infection may still remain in ARQ animals and provide a potential source of adaptation to new strains of TSEs.

**Overall conclusions**

47. The Sheep Subgroup agreed that the prevalence of BSE in the UK sheep population is most likely to be zero, or very low if present at all. Consequently any impact of the RGS on human health from removing BSE from sheep is likely to be negligible. Furthermore, current surveillance, if maintained, together with risk reduction methods such as SRM controls and the MBM feeding ban, would minimise the risk of an extensive epidemic and to human health were BSE in the future ever to enter the UK sheep flock.

48. It broadly concurred with the conclusions expressed in the EFSA Opinion on breeding for resistance in sheep. However, it concluded that EFSA conclusions regarding the effect of the current breeding programme on the prevalence of atypical scrapie were premature. The Subgroup reiterated its position statement on atypical scrapie and recommended that a watching brief should be kept on research into the experimental transmission of atypical scrapie to humanised mice. The implications of results of such studies should be debated in advance.

49. It concluded that the scientific basis underpinning the current RGS remains valid to remove a large proportion of classical scrapie infection. However classical scrapie infection may remain in ARQ sheep, which are also susceptible to BSE and could provide a

reservoir for future infection. A combination of flock culling and repopulating with appropriate genotypes in scrapie infected flocks would be the best approach to eliminate classical scrapie from the UK flock.

50. It agreed that, given the increasing number of PrP polymorphisms identified, an understanding of the genotype profile of the national sheep population could form a basis for any future TSE control strategies, for example emergence of a new TSE, and ensure a ready supply of rams of appropriate genotype if repopulation of TSE affected flocks is ever required. In addition to codons 136, 154 and 171, codons 141 and 168 also appear to influence TSE susceptibility and this should be taken into account.

**Advice sought from the Sheep Subgroup regarding WEGS**

51. The Sheep Subgroup recognised that, at the outset of RGS and WEGS, the genotype profile of the Welsh sheep flock had been at a disadvantage regarding susceptibility to classical scrapie compared to the rest of GB.

52. It recognised that hill breeds were predominant in the Welsh flock and were at the most risk from classical scrapie. The Subgroup noted that substantial progress had been made through the RGS and WEGS to breed for scrapie resistance in the hill breeds and that WEGS had accelerated the progression towards the more scrapie-resistant genotypes.

53. The genotype profile of the Welsh sheep flock had largely caught up with the rest of GB in the proportion of the more scrapie resistant genotypes. Although there were still a significant number of scrapie cases in Wales, this may reflect a larger sheep population and the prevalence may not now be significantly different from that in the rest of GB.

54. The Sheep Subgroup concurred with the proposal to project the proportion of resistant and semi resistant genotypes in flocks in Wales to 2013 and beyond as a result of RGS and WEGS II by modelling the following scenarios:

- no RGS and/or WEGS from 2007 onwards,
- where RGS and WEGS membership remains at levels for 2005/06, to 2013 and beyond,
- where RGS membership remains at current levels but WEGS is

terminated in March 2008,

- where RGS membership is 125%, 50% and 25% of levels for 2005/06 with WEGS terminated in March 2008

55. The Subgroup was asked for its opinion on a proposed survey to establish the genotype distribution of lambs born in 2006 on holdings in Wales entering the food chain. This 2006 genotyping of finished lambs would also seek to provide baseline data to assess and evaluate progress in the future.

56. The Subgroup agreed this genotyping should be maintained and that it might be beneficial to include codons 141 and 168 in the programme, as well as codons 136, 154 and 171.

57. The Subgroup agreed that the general conclusions regarding RGS also apply to the Welsh sheep flock. It concurred that the Welsh sheep flock is no longer at a disadvantage compared to the rest of GB with respect to susceptibility to classical scrapie. Thus, there may no longer be a case for considering Welsh sheep differently from the rest of the UK. Thus, the current situation is that the risk of BSE in sheep is likely to be zero, with a consequent reduction in the perceived risk to public health although there are uncertainties regarding atypical scrapie.