



**COMMITTEE MEMBERS' BRIEFING FOR PUBLIC Q & A SESSION
AT SEAC 94, 21ST SEPTEMBER 2006**

Note:

This document was originally produced to remind SEAC members of key points that could be used as the basis for answers to questions at the SEAC 94 public Q&A session (September 2006). This document is by no means exhaustive. [Annual reports](#) and [meeting pages](#) should be viewed for a detailed view of items discussed at SEAC meetings.

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SEAC - THE COMMITTEE

SEAC's terms of reference

To advise Ministers on Transmissible Spongiform Encephalopathies (TSEs) at the request of:

Department for Environment, Food and Rural Affairs
Department of Health
Food Standards Agency
Scottish Executive
Welsh Assembly Government
Northern Ireland Executive

To provide independent scientific advice on food safety, public and animal health issues relating to TSEs taking account of the remits of other bodies with related responsibilities.

To provide scientifically based assessment of risk from TSEs to public and animal health and food safety taking appropriate account of scientific uncertainty and assumptions in formulating advice. The committee will convey the nature and extent of such uncertainties with the advice.

To advise on important general principles or new scientific discoveries in TSEs to assist in the identification of new or emerging TSE risks for public, animal health and food.

To advise on the scientific basis and risks associated with the introduction of new control measures or the reduction, phasing out or withdrawal of current control measures which are in place to protect public health or animal health from TSEs.

To identify where research is desirable to reduce the scientific uncertainty and inform the assessment of public and animal health and food safety risks relating to TSEs.

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Content and purpose of this document

This briefing document provides a summary of SEAC's discussions and conclusions on a range of issues considered since 2004.

Its purpose is to remind committee members of key points that could be used as the basis for answers to questions in the public Q&A session at the end of the morning session at SEAC 94.

The annex of this document also includes the minutes from two previous public Questions and Answers sessions. These are included as examples of the type of question that may be raised and the responses given by SEAC members.

Committee members are reminded that SEAC's remit is restricted to issues of scientific risk assessment.

Officials from Defra, DH and the FSA should be invited to contribute to the discussion if questions of risk management or Government policy arise.

Committee members are free to address questions raised at the public Q&A from a personal point of view provided they make it clear that they are not speaking on behalf of SEAC.

CJD AND PUBLIC HEALTH

Profile of the vCJD epidemic

At SEAC 86 (March 2005), SEAC tasked the SEAC epidemiology subgroup to conduct an assessment of the future profile of the vCJD epidemic. At SEAC 90 (November 2005) the subgroup reported back to SEAC.

Background

Incidence of vCJD has declined over the past 4 years in the UK¹. Projections based on the case data suggest the number of additional cases of vCJD arising from the consumption of BSE-infected material might be relatively small (less than 100). However, findings from a retrospective survey of appendix and tonsil tissue from operations carried out between 1995 and 2000 on individuals predominantly (83%) in the age range 10-30 years suggest that the number of infected individuals may be greater than projections based on back calculation from vCJD cases suggest. Furthermore, research in animal models suggests it is possible that a proportion of infections may not develop into clinical disease, or do so over a longer time scale, and remain at a subclinical level. Although all vCJD cases tested to date (about 85% of cases) have been of the M/M genotype at the polymorphic codon 129 of the human prion protein gene, the effect of other genotypes on the susceptibility to, infectiousness of, and phenotype of, vCJD is uncertain. The finding of an asymptomatic case of probable blood transfusion associated transmission of vCJD of the M/V genotype suggests individuals of this genotype are also susceptible to secondary transmission by the intravenous route. It is possible that secondary infection via medical procedures may give rise to additional infections and potentially enable a self-sustaining secondary epidemic.

On the basis of the position statement SEAC concluded that:

- a substantial number of subclinical carriers of vCJD infection may exist in the UK. As such a secondary, possibly self-sustaining, vCJD epidemic could arise due to medical practices.
- there is an urgent need to ascertain better the prevalence, age and genotype distribution of subclinical vCJD infection in the UK in order to implement appropriate precautionary measures. Planned testing of samples under collection for the National Anonymous Tonsil Archive (NATA) should proceed with urgency.

¹ Number of deaths from vCJD in the UK in the years 1999 to 2005: 15 (1999), 28 (2000), 20 (2001), 17 (2002), 18 (2003), 9 (2004) and 3 (end September 2005).

- it is important that additional programmes concentrating on older populations are considered as a large proportion of tonsils from the NATA will be from young individuals with relatively low dietary exposures to BSE.
 - the testing of tissues collected from autopsies could potentially provide substantial data on the prevalence, age and genotype distribution of infection. DH should urgently convene an expert group to consider the practical, ethical and legal issues around post mortem testing in the UK.
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Risk of vCJD transmission via surgery

At SEAC 84 (September 2004) the committee considered an updated version of the DH's risk assessment of vCJD transmission via surgery.

The following points were noted:

- there have been no definite or suspected cases of vCJD transmission between humans via surgery.
 - SEAC considers there is a theoretical risk of transmission of vCJD through the use of contaminated surgical instruments.
 - there is some epidemiological evidence of iatrogenic transmission of sCJD via instruments used in neurosurgery.
 - vCJD infectivity is more widespread in the body compared with sCJD.
 - although the theoretical risk could depend on a number of factors, it is likely to be greatest from operations involving the CNS and ophthalmic tissue, followed by lymphoid tissue.
 - SEAC considers that rigorous implementation of effective washing and decontamination procedures are key measures in minimising theoretical risks of infection.
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Methods to Evaluate new Surgical Instrument Decontamination Technologies

At SEAC 93 (July 2006) the committee was asked by the 'Engineering and Science Advisory Committee into the decontamination of surgical instruments including prion removal' (ESAC-Pr) to advise on the principles to consider when developing strategies to evaluate new decontamination technologies of surgical instruments.

Background

Residual biological material, including protein, can remain adherent to the surface of surgical instruments following current recommended cleaning, disinfection and sterilisation procedures. Prions adsorbed onto stainless steel surfaces are unusually resistant to normal decontamination practices and, although achieving very significant reductions in prion load, conventional procedures do not completely remove or inactivate prions on surgical instruments. Therefore, infectious material may be transferred from an infected patient to other patients via surgical instruments. A small number of cases of sporadic Creutzfeldt-Jakob disease (sCJD) transmission via contaminated surgical instruments have been reported.

To date, no cases of variant Creutzfeldt-Jakob disease (vCJD) transmission via surgical instruments have been reported. However, the risks of vCJD transmission may be significant for surgical procedures involving the central nervous system (CNS), posterior eye and lymphoid tissue. Effective instrument decontamination is critical to reducing these risks.

A number of new decontamination technologies are claimed to remove, degrade and/or deactivate prions adsorbed onto surgical instruments. These claims are based on extrapolation of results from laboratory studies using experimental systems to model the clinical situation. However, a standardised system to evaluate and compare the effectiveness of decontamination technologies has not yet been defined.

SEAC Conclusions

- Independent and quantitative evaluation of the effectiveness and reliability of new decontamination technologies prior to their implementation is strongly recommended. Evaluation strategies should be standardised and include quantitation of the effect of treatments on the infectivity of vCJD, or closely related, prions adhering to stainless steel.

- It is also recommended that research is conducted to examine the relative resistance to decontamination of stainless steel contaminated with wet compared with dried-on material.
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Endodontic Dentistry and vCJD

At SEAC 91 (February 2006) the committee reviewed new information on the potential risks of vCJD transmission via endodontic dentistry (dental procedures involved in the maintenance of dental pulp and the treatment of the pulp cavity).

There are no reported definite or suspected cases of vCJD transmission arising from dental procedures.

SEAC concluded that:

- a preliminary risk assessment produced by DH suggests vCJD transmission via endodontic dentistry may, under certain hypothetical but plausible scenarios, be sufficient to sustain a secondary vCJD epidemic. However, there are uncertainties around the data and assumptions underpinning the assessment. Research underway will address some of these uncertainties and allow the risk assessment to be refined. Once the research is complete and / or other data become available, the risks should be reassessed. A watching brief should be maintained.
 - it is unclear whether or not vCJD infectivity can be transmitted via endodontic files and reamers. However, given the plausibility of such a scenario and the large number of procedures undertaken annually, it would be prudent to consider restricting these instruments to single use as a precautionary measure. Since sufficiently rigorous decontamination of these instruments is difficult, single use of these instruments would eliminate this risk, should it exist.
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Transmission of prion diseases by blood transfusion

Probable cases of blood transfusion-associated transmission of vCJD

SEAC was informed of three cases of blood transfusion associated transmission of vCJD at SEAC 81, 83 and 91 (February 2004, June 2004 and February 2006).

First Case.

The Transfusion Medicine Epidemiology Review (TMER) identified a case of possible transmission of vCJD by blood transfusion. The recipient received non-leucodepleted red blood cells in 1996 from a donor who, at the time of donation, was free of clinical signs of vCJD, although went on to develop vCJD in 1999. The blood recipient died of vCJD in 2003.

Second Case

An elderly patient died in 2004 showing no clinical signs of vCJD with death from an unrelated cause. The patient had received a single unit of non-leucodepleted red blood cells in 1999 that had been donated by an individual who was confirmed in 2001 as a definite vCJD case. The donor's disease onset was in 2000. There was no evidence of a spongiform encephalopathy and prion protein accumulation was detected in the spleen and a cervical lymph node. The case was methionine/valine at codon 129 of the PrP gene.

Third Case

The case developed symptoms of vCJD approximately 8 years after receiving a non-leucodepleted blood transfusion from a donor, who had developed symptoms of vCJD about 20 months later.

In reviewing the three cases the Committee noted:

- in light of these three cases there is a relatively high risk of transmission of vCJD by blood transfusion.
- it should be a public health priority for all recipients of blood (leucodepleted or not) from donors incubating vCJD to be subject to the kind of careful post-mortem examination that had been possible in this case. This would help to quantify the nature and magnitude of the risks of transmission of the vCJD agent through blood donated by preclinical cases of vCJD.

- that active approaches to obtaining tissues for testing and clinical monitoring of these patients was important both to ensure best practice clinical care and enhancing understanding of risks.
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Early phase of vCJD infection in recipients of blood transfusions

At SEAC 87 (April 2005), the Committee on Microbiological Safety of Blood, Tissue and Organs asked SEAC whether:

- a scientific distinction could be drawn between historic and recent blood transfusion recipients in terms of the relative load of the vCJD agent that may be present in the bone, tissues or organs of the blood transfusion recipient.

In the context of this question, a recent recipient was defined as having received a blood transfusion within the week prior to bone, tissue or organ donation. A historic recipient was defined as having received a blood transfusion in the more distant past.

SEAC noted that:

- recipients of blood products from vCJD cases had been notified and deferred from tissue/organ donation. All recipients of tissues/organs were also deferred from blood transfusion.
- until sensitive ante mortem tests, especially for blood, become available it may not be possible to conduct definitive experiments that would further inform assessment of the transplant associated risks of vCJD transmission.

SEAC concluded that:

- because of a small background risk of vCJD infection in the population as a whole, tissues/organs from donors that had not received a blood transfusion carried some risk of vCJD transmission.
- there is no clinical evidence that vCJD has been transmitted through tissue/organ transplantation. However, a potential risk of transmission via this route exists. Relevant data are extremely limited but suggest that in the early phase of infection, significant prion replication is unlikely to occur and that, therefore, tissue levels of abnormal prions following recent transfusions are likely to be related to the blood supply to each specific tissue.

- a risk of transplant-associated transmission of vCJD exists from tissue/organ donors that have not received blood transfusions. The additional risk as a result of a donor having received a recent blood transfusion is likely to be very small. Post mortem assessment of donor infection would provide the best method of risk reduction and enable these risks to be quantified.
- in assessing and communicating the risks a balance must be struck between the small risk of vCJD transmission by transplantation and the benefits to patients receiving a transplant, especially where tissues/organs are scarce and are required for (potentially) life-saving procedures.

vCJD Infectivity in Blood

At SEAC 90 (November 2005) SEAC reviewed published information in relation to the key assumptions made in the assessment of exposure to vCJD infectivity in blood and blood products published in 2003 by Det Norske Veritas Consulting (DNV).

SEAC considered that all the following key assumptions made in the DNV assessment appear still to be reasonable:

- Blood from people incubating vCJD is infective.
- Infectivity is constant throughout the incubation period.
- Infectivity of blood from vCJD cases is 10 ID₅₀/ml.
- Intravenous route is 5 times less efficient than the intracranial route.
- Incubation period for vCJD derived from blood is 15 years.
- All people are assumed to be vulnerable to infection by vCJD, genetic variations will only affect incubation period.
- Split of infectivity between blood components is: 24% in red cells, 22% in buffy coat (leucocytes and platelets) and 54% in plasma.
- Dose-response function for vCJD infectivity is linear with no threshold.

SEAC strongly recommended that robust research is undertaken to examine infectivity levels through the incubation period and the distribution of infectivity in blood components.

At SEAC 92 (April 2006) the committee reviewed unpublished data which allowed some of the assumptions of the (DNV) risk assessment to be reconsidered.

The specific issues considered were: the relative levels of TSE infectivity in whole blood and in each of the individual blood components, the change in the level of TSE infectivity in blood over the course of the incubation period of disease, the relative efficiencies of the intracranial and intravenous routes of inoculation and the dose-response relationship for infection by a TSE. A position statement was produced as a result of the discussion.

SEAC Concluded that:

- the available data show that blood is infectious during the preclinical stage of vCJD. Although the precise time in the incubation period of vCJD at which blood becomes infectious is unclear, data from animal models suggests it may be infectious from at least, if not before, the middle of the incubation period.
 - the source of infectivity in blood is not understood. Data from rodent studies suggests that infectivity in whole blood is around 10 ID/mL and that it mostly resides in the plasma and white blood cell components with infectivity associated with white blood cells substantially depleted by extensive washing.
 - additional information from other animal models is required to assess whether the rodent findings may be closely representative of vCJD infectivity in human blood. It is clear that an infectious dose in blood can be disseminated but not diluted by distribution to a large number of recipients.
 - pooling of potentially infectious material, or in other ways disseminating infectious material between a number of recipients, will not reduce the number of people infected, and is likely to increase the number of people infected.
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Mouse models of human to human transmission of vCJD

At SEAC 90 (November 2005) SEAC were informed of ongoing research into the effect of genotype on human-to-human transmission of vCJD using humanised transgenic mice. The species barrier between humans and cattle was also examined.

SEAC concluded that:

- the species barrier for secondary transmission of vCJD between individuals may be much lower than the species barrier for primary transmission of BSE from cattle to humans.
- individuals of M/V and V/V genotypes are likely to be susceptible to vCJD infection, although they may be less susceptible to clinical vCJD, exhibit a different neuropathological phenotype, and longer incubation periods compared with individuals of the M/M genotype.
- subclinical infection carrier state is influenced by genotype.
- there is an urgent need to assess the true prevalence of vCJD infection if appropriate management of potential secondary infections is to be implemented.

Lack of correlation between abnormal prion protein concentrations and infectivity

At SEAC 90 (November 2005) SEAC were informed of ongoing research into the relationship between infectivity and PrP^{Sc} concentrations.

SEAC concluded that:

- the research suggested there was no clear correlation between abnormal prion protein concentrations and the titre of TSE infectivity in some animal models. The committee considered that the precise role of abnormal prion protein in relation to the infectious and neurodegenerative properties of TSE agents remains unclear.
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Prion reduction filters

At SEAC 91 (February 2006) the UK blood services (UKBS) prion reduction group asked the committee to comment on the methodologies used to validate prion reduction filters, this follows the SEAC recommendation that an independent validation of the filters should be performed.

The committee concluded that:

- the UKBS should commission an independent validation of such products.
 - filters be evaluated on both leucodepleted and non-leucodepleted blood, since if they worked well on non-leucodepleted blood it may be possible to remove the leucodepletion step.
 - blood from individuals considered 'at risk of vCJD' should be collected with ethical approval and patient consent.
 - it was important to replicate the experiments that the filter manufacturers performed to test the efficacy and reproducibility of the filters.
 - further experiments to evaluate the filters should include the use of an additional rodent strain and different forms of inoculum. These experiments would provide indication of differences in the efficacy of filters against different strains or TSE agent. It is critical to include the BSE agent in these studies. Experiments that tested the removal of endogenous infectivity were important and that it was crucial to develop a model that was as close as possible to the human situation.
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Medical Implants Containing Bovine Material

At SEAC 91 (February 2006) the Medicines and Healthcare products Regulatory Agency (MHRA) asked the committee to consider the potential BSE risks to humans from medical implants using bovine material from the USA.

The regulations on medical devices containing animal materials are based on the principle that TSE risks must be eliminated or reduced as much as possible and residual risks must be acceptable when weighed against the benefits to patients. Currently no guidance exists on the acceptability of TSE risk control measures applied to animal material in medical devices.

The MHRA requested advice on three 3 issues. (i) can TSE risk associated with medical implants using USA sourced bovine material be estimated given that it might vary over time? (ii) is there, or has there been a significant risk that might warrant action in addition to that already taken? (iii) can the standards that support the regulations be altered to facilitate a consistent approach about the acceptability of products?

The committee concluded that:

- a risk assessment should be conducted on each device because of the large number of variables that influence associated TSE risks.

Key factors which should be considered when assessing risks are:

- the animal source. Use of material from closed herds or from herds that are managed carefully to prevent the introduction of the BSE agent.
- use of material from young animals would markedly lower risk compared with older animals.
- the geographical risk of BSE. The geographical BSE risk status of a country gives an imprecise indication of BSE risk. It would be better to use an estimated prevalence of BSE in a country based on data from a robust surveillance system.
- the potential TSE infectivity of the source tissue(s) based on a careful assessment of the available data on tissue infectivity.

- the site of implantation. Sites with contact with the blood supply or CNS may increase risk.
 - whether TSE testing is undertaken on the source animal(s).
 - the number of source animals used for each device.
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Transmission of vCJD from mother to child via human breast milk

At SEAC 85 (November 2004), the CMO for England asked SEAC to:

- consider current evidence and comment on the potential transmission of vCJD from mother to child via human breast milk.

SEAC concluded that:

- there is currently no epidemiological evidence for maternal transmission of vCJD, including transmission via breast milk. However, there is a hypothetical risk.
- although available evidence is limited and mostly indirect rather than direct, this risk, if any, appears to be low.
- as a risk cannot be excluded, a watching brief should be maintained.

FOOD SAFETY

Abnormal prion protein in bovine milk

At SEAC 88 (June 2005) the FSA asked the committee to consider the results of research to develop diagnostic tests to detect BSE infection-associated abnormal prion protein (PrP^{BSE}) in cows' milk and to screen milk which had been collected previously from cattle experimentally infected with BSE for the presence of PrP^{BSE}.

The committee:

- considered the study to be well designed and carefully conducted.
- agreed that the study showed no evidence for the presence of PrP^{BSE} in milk of experimentally infected cattle, within the limits of detection of the test methods used.
- noted that there is no published evidence for the presence of BSE infectivity in udder tissue.
- concluded that the results of this study, together with the findings of previous epidemiological and experimental research (particularly no specific persistence of BSE in suckler herds), provided no evidence for the presence of PrP^{BSE} in, or for transmission of BSE via, milk.

Detection of abnormal prion protein in some tissues of the peripheral and central nervous systems of cattle with BSE

At SEAC 89 (September 2005) and at SEAC 93 (July 2006), SEAC discussed research on the detection of abnormal prion protein and infectivity in some tissues of the peripheral and central nervous systems (PNS and CNS) of BSE cases.

SEAC concluded that:

- low levels of PrP^{Sc} in PNS tissues could be detected at the same time, or after, PrP^{Sc} was detected in the CNS.
- the level of infectivity detected in PNS tissue was considerably lower than in CNS tissue.

- the data so far did not warrant re-examination of the risk under the current SRM regulations.

Over Thirty Months Rule (OTMR)

The Over Thirty Months Rule was replaced by a BSE testing regime on 7th November 2005.

Summaries of the main points from SEAC's recent discussions on risk assessments relevant to the OTMR change are given below.

Over Thirty Months Rule change: BSE exposure risk from vertebral column

At SEAC 87 (April 2005), the FSA asked the committee to review an assessment of the BSE exposure risk from vertebral column².

Background

In 1997, the Ministry of Agriculture, Fisheries and Food had imposed a ban on beef on the bone in the UK on the basis of SEAC advice that there was a small risk that prion infectivity could be transmitted to humans through consumption of residual dorsal root ganglia (DRG) associated with the vertebral column. In 2000, the ban had been lifted for discrete cuts of meat from under thirty month cattle, where bone was obviously present, but not for processed meat products. Thus, consumers could choose to eat beef on the bone.

Under EU TSE regulations current in April 2005, the vertebral column of cattle over 12 months was classified as specified risk material (SRM). The UK had a derogation whereby vertebral column was classified as SRM for cattle aged over 30 months. The UK derogation had been authorised due to the UK demonstrating the effectiveness of restrictions placed on animal feed, and on the basis that UK beef was not exported. Recently the European Food Safety Authority (EFSA) had indicated that the UK BSE status may be re-categorised from "high risk" to "moderate risk". This would allow beef exports to resume, but only if the UK adopted the same TSE rules as other EU member states. EFSA would be conducting a risk assessment on harmonising rules on the SRM age limit for vertebral column.

² DNV Consulting (2005). Assessment of Risk from Under Thirty Month Beef-on-the-Bone: Report for the Food Standards Agency,

In view of this, the FSA had commissioned DNV Consulting to assess risk from under thirty-month beef on the bone, which would be presented to EFSA. This risk assessment quantified the infectivity predicted to enter the human food chain over a year as a result of making vertebral column specified risk material (SRM) at the age of 12 months instead of 30 months.

SEAC considered that:

- the human health risk from vertebral column in under thirty month cattle was now very small. The difference in risk from vertebral column as SRM at 12 as opposed to 30 months of age was negligible.

SEAC noted that:

- members were content with the approach used and assumptions made in the risk assessment.
 - some uncertainties remained with regard to the extent of the species barrier between cattle and human. Nevertheless, even using the most pessimistic assumption (i.e. low species barrier), the overall conclusions would not be significantly altered.
 - the assessment included a pessimistic assumption about the levels of infectivity entering the food chain from residual dorsal root ganglia associated with vertebral column.
 - the risks to any subpopulation consuming large amounts of UK beef had not been specifically considered. Data on specific groups who might consume significant amounts of beef on the bone were not available. Nevertheless, although exposure would be higher in any such group than assumed in the assessment, it was considered that the risk to this population group is still likely to be very small.
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Over Thirty Months Rule change: summary of SEAC's discussion on conclusions from the FSA/SEAC Risk Assessment Group

At SEAC 82 (April 2004), the FSA asked the committee to comment on the conclusions reached by the FSA / SEAC Risk Assessment Group (RAG).

Background

RAG had been convened to provide scientific advice to the FSA on the levels of risk to the consumer from changes to the Over Thirty Month Rule. At its meeting earlier in April 2004, RAG had considered the impact of new data on the OTMR risk assessment. These data included the vCJD case likely to have resulted from blood transfusion and results from the retrospective tonsil / appendix study funded by the Department of Health.

SEAC's discussion

In terms of impact of the new data on the OTM Rule review risk assessment, both SEAC and RAG

- agreed that the new data do not alter the fundamental assumptions used to assess the effect of OTM rule removal (i.e. in estimating the ratio of future risk to that from past exposure).
- agreed that it was unlikely that the new data on the possible risk of transmission of vCJD through blood transfusion would have an important impact on the risk assessment.
- agreed that the finding of a case of BSE in the US and the report of atypical cases of BSE in Italy would be most unlikely to have any impact on the risk assessment.
- acknowledged the significant disparity between the recent prevalence data and model predictions based on the clinical case data.
- agreed that replacing the OTMS with testing to identify BSE infections in OTM cattle would have only a very small effect on the estimated potential overall size of the vCJD epidemic.

Divergence of scientific opinion

Some SEAC members agreed with RAG's approach. However, others considered that the new appendix data should be given most weight, despite the significant uncertainty in interpreting these data. They

thought it was more appropriate to adopt a cautious approach and derive a pessimistic estimate based on the prevalence data alone and assume that all three individuals would go on to develop clinical vCJD. Thus, the divergent opinions between RAG and some SEAC members stemmed from a difference in the weight given to the different data sets rather than a fundamental disagreement *per se*.

Both SEAC & RAG agreed that if a pessimistic estimate were to be based on the prevalence data alone, it would lead to a small corresponding increase in the potential number of future vCJD cases arising from the OTM rule change.

After the meeting, SEAC issued a statement summarising the RAG and SEAC considerations.

Over Thirty Months Rule change: OTMR review risk assessment

At SEAC 83 (June 2004), the FSA asked the committee to consider further modelling work by Imperial College London that compared the risks of different changes to the OTMR. Options for changes included allowing only healthy or a combination of healthy and casualty animals over thirty months old into the food chain, subject to the EU BSE testing requirements. This analysis utilised the estimates of the human exposure to BSE previously considered by SEAC, and an integrated estimate of the size of the vCJD epidemic based on the case data and the new data from the retrospective tonsil/appendix study³. The modelling showed that removal of the OTMR would result in very small numbers of future vCJD cases, relative to the size of the overall epidemic.

The committee:

- was content with the approaches used and noted that pessimistic assumptions had been incorporated in the modelling work. These included assumptions that the future BSE infection risk for cattle would remain constant at the level in 1999, the low sensitivity of TSE diagnostic tests prior to the onset of clinical disease and the similar susceptibility of all human PrP genotypes to infection.
- noted that the inclusion of casualty animals increased the level of risk disproportionately to the number of casualty animals entering the food supply.

³ Hilton DA *et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol.* 2004 203, 733-739.

- recommended that the FSA Board note this when considering risk management options for changes to the OTMR.

After the meeting, SEAC issued a statement summarising the assessment of the future number of vCJD cases arising from relaxation of the OTM scheme.

The effect of chronic inflammation on tissue distribution of scrapie prions and infectivity – the findings of Heikenwalder *et al*

At SEAC 86 (March 2005), the FSA asked the committee to discuss a recent paper⁴ which reported that in mouse models, chronic inflammation altered the tissue distribution of scrapie prions and infectivity. In these mice, scrapie prions and infectivity had been detected in tissues not normally infective.

SEAC was asked to consider:

- the implications of the findings for specified risk material (SRM) controls which prevent animal tissues known to be potentially infective reaching the human food chain.

The committee noted that:

- the immune system of the mice had been genetically modified resulting in very specific and severe forms of inflammation which may not reflect conditions that normally apply on the farm. Thus, it would be premature to conclude that such inflammation altered the effectiveness of SRM controls.
- inspections of animals at abattoirs restricted the entry of unhealthy animals into the food chain. Thus, animals with severe inflammation should normally be excluded from the food chain.

The committee agreed that:

- the findings were very interesting and that further work would be required to investigate more fully the influence of inflammation on prion disease and infectivity.
- nevertheless, to minimise potential risk, the Meat Hygiene Service should continue to be particularly vigilant in this area.

⁴ Heikenwalder *et al.* (2005) Chronic lymphocytic inflammation specifies the organ tropism of prions. *Science*. 307, 1107-10.

Detection of Abnormal Prion in the Mammary Glands of sheep.

At SEAC 90 (November 2005) a report⁵ on the detection of abnormal prion in the mammary glands of five Italian farmed Sarda sheep with coincident clinical signs of natural scrapie and mastitis was considered.

SEAC concluded that:

- Sarda sheep in this study had a specific type of mastitis not seen in the UK.
- it was unclear whether the sheep had clinical or subclinical mastitis since the mastitis agent involved did not lead to a greatly increased cell count in milk and was therefore difficult to diagnose.
- there is some consumption of sheep milk and milk products in the UK. Legislation precludes milk from animals with clinical mastitis entering the food chain, however this would not be effective in sub-clinical disease.
- this was an important study, demonstrating the presence of abnormal PrP^{Sc} in unusual sites in sheep with two concurrent diseases.
- it would be important to consider the results of further work and whether other secondary infections might alter PrP^{Sc} distribution in prion infected animals.

FSA contingency policy for possible BSE in sheep

At SEAC 84 (September 2004), the FSA asked SEAC to advise on the underlying scientific assumptions and approaches adopted in two modelling studies to inform the FSA's contingency policy should BSE ever be found in sheep.

The modelling studies, based upon discriminatory testing of a large number of samples from scrapie suspects by the VLA together with published and unpublished data on the pathogenesis of BSE and scrapie in sheep, examined the possible prevalence of BSE in sheep

⁵ Ligios *et al.* (2005) PrP^{Sc} in mammary glands of sheep affected by scrapie and mastitis. *Nature Medicine* 11, 1137-1138.

and the likely impact of different risk reduction strategies if BSE was found in sheep.

In addition to discussing the modelling studies, the committee considered the analytical methods used to discriminate BSE and scrapie in sheep.

The committee:

- considered that tests to distinguish BSE from scrapie had limitations but were becoming more robust. Studies to date showed no evidence for BSE in UK sheep.
- acknowledged the theoretical nature of the modelling work and that modelling the possible impact of BSE in sheep if it entered the national flock was complex. Due to the very limited data available, the models had necessarily relied heavily on many assumptions. In particular, the modelling assumed that BSE and scrapie would behave similarly in all types of sheep, which is largely unknown.
- noted that the modelling indicated that a single BSE infected sheep entering the food supply could present a significantly greater risk compared to the current risk from a single infected bovine.
- noted that the model suggests that a risk reduction strategy based on the PrP genotype of sheep would be the most effective, if BSE were found in the national flock.

Chronic Wasting Disease (CWD) and BSE in UK deer

At SEAC 85 (November 2004) and SEAC 93 (July 2006) the committee considered the possible public and animal health implications of chronic wasting disease (CWD).

SEAC concluded that:

- there is no evidence that CWD (or BSE) is present in the UK cervid population but a low prevalence could not be ruled out. Because only limited surveillance had been conducted, SEAC recommended that further surveillance of TSEs in UK cervids is conducted.

- there is no evidence of transmission of CWD to humans from consumption of meat from infected cervids however, CWD infectivity has been found in the muscle of mule deer.
- although epidemiological and experimental data on potential transmission of CWD are extremely limited, they suggest that there may be a significant species barrier. It would be helpful if further studies were available assessing the potential species barrier for transmission to humans.
- although limited, there is no evidence CWD can be transmitted to cattle, sheep or goats by natural means.
- there is evidence that more than one strain of CWD may exist.
- research shows that CWD may be transmitted through contaminated soils.
- although there was no evidence that CWD was a human health risk, SEAC asked that a watching brief be maintained.

The European Commission TSE Roadmap

At SEAC 89 (September 2005) and SEAC 93 (July 2006), Defra and FSA asked the committee to consider the European Commission's seven strategic goals for the short and medium term (2005-2009):

1. To ensure and maintain the current level of consumer protection by continuing to assure the safe removal of specified risk material (SRM) but modify the list and age of removal based on new and evolving scientific opinion.
2. A relaxation of certain measures of the current total feed ban when certain conditions are met.
3. To reduce the number of tests of bovine animals and at the same time continue to measure the effectiveness of the measures in place with a better targeting of the surveillance activity.
4. Simplification of the categorisation criteria and conclusion of the categorisation of the countries before 1 July 2007.
5. Review and relaxation of the eradication measures for small ruminants taking into account the new diagnostic tools available but ensuring the current level of consumer protection.
6. To stop the immediate culling of the cohort in bovine animals.
7. To discuss the lifting of the additional restrictions on exports of beef and beef products from the UK if there is compliance with preset conditions.

SEAC was asked to advise whether:

- for each of the strategic goals, the Commission had identified all of the risk issues that needed to be taken into account when considering changes to current control measures.
- any additional existing evidence or results of work in progress would be required for SEAC to provide, when needed, an assessment of the risks from specific regulatory changes.

SEAC commented that:

- changes to legislation in any one of the strategic areas might impact on other areas, therefore no single strategic area should be considered in isolation.
- appropriate feed controls are fundamental to prevent recycling of potentially infectious material in animal feed and re-emergence of a BSE epidemic.
- surveillance to ascertain infection prevalence was very important as a public health protection measure and an effective system should be maintained.
- there should be a watching brief on emerging science that may impact on any of the measures under consideration.
- in the event of any changes to TSE legislation it would be important to communicate effectively to consumers the reasons for change.

Defra and FSA will seek SEAC advice on future proposals arising from the European Commission TSE Roadmap.

ANIMAL HEALTH

The hypothesis (by Colchester & Colchester) that BSE originally derived from a human TSE

At SEAC 89 (September 2005), the committee discussed a paper by Colchester & Colchester⁶ presenting a hypothesis that BSE was originally derived from a human TSE. The hypothesis suggested that, in the 1960s and 1970s, mammalian bone and carcass material used in animal feed was imported into the UK from the Indian sub-continent, particularly the area around the Ganges, and contained remains from humans infected with CJD.

SEAC concluded that:

- it is unlikely that the origins of BSE would ever be determined conclusively.
- it is not possible to determine, from current knowledge of the characteristics of prion strains, whether BSE originated from CJD or other animal prion strains.
- there was evidence to suggest that human remains may have been included in animal feed derived from the Indian subcontinent in the past, and the hypothesis presented by Professor Colchester was therefore considered plausible, but ultimately untestable.
- historically very much larger quantities of cattle and sheep remains had entered animal feed, compared with putative human remains. There is also likely to be a significant species barrier between humans and cattle, as there is known to be such a barrier in the opposite direction. It is therefore very much more likely that the origins of BSE are related to a TSE that originated in cattle or sheep, rather than a TSE from humans.
- although Professor Colchester's hypothesis can never be ruled out, SEAC considered that, on the balance of possibilities, human TSE-contaminated material in animal feed was unlikely to have been the origin of BSE.
- current control measures now prevent possible transmission via the route proposed in this hypothesis.

⁶ Colchester and Colchester (2005). The origin of bovine spongiform encephalopathy: the human prion disease hypothesis. *Lancet*. 366, 856-61.

The hypothesis that toxic alkaloids in ryegrass may have been a contributing factor in the BSE epidemic

At SEAC 87 (April 2005), the committee was informed that a number of members had commented on a submission from a member of the public hypothesising that toxic alkaloids in ryegrass may have been a contributing factor in the BSE epidemic.

Committee members agreed that:

- the evidence put forward in support of this hypothesis was not sufficiently rigorous or compelling to warrant a full discussion.
- the evidence that contaminated meat and bone meal was the primary cause of BSE epidemic remains strong and the information provided did not persuade SEAC to alter this view.

The committee stressed that:

- it welcomed submissions of evidence on alternative hypotheses for the causes or origins of BSE provided that there were sufficient supporting data to allow hypotheses to be discussed.

Differential diagnosis of BSE

At SEAC 88 (June 2005), the committee discussed:

- Defra's approach to differential diagnosis of BSE
- Defra's approach to enabling the detection of atypical forms of BSE or other unknown or associated diseases in cattle.

Background

The discussion had been stimulated by earlier observations that a decreasing proportion of cattle identified by surveillance as showing clinical signs attributed to BSE had been confirmed subsequently as BSE positive.

The committee:

- acknowledged that, given the large number of clinical conditions that might resemble BSE, it was disproportionate to attempt to

definitively diagnose all suspect BSE cases that are not confirmed as BSE.

- acknowledged the measures taken by Defra to ensure that BSE ascertainment is maintained in the field (including a DVD on differential diagnosis that had been sent to vets for training purposes).
- emphasised that it is not unreasonable to expect that 'atypical' cases of BSE might arise, given reports from other countries and recent evidence for 'atypical' scrapie.
- considered it was crucial to ensure that atypical cases of BSE, should they occur, would not be missed. With this in mind, it would be appropriate to collect appropriate tissue samples in addition to obex, and to ensure application of the most appropriate methodology as it develops.

Nomenclature and Use of the Term “Atypical” to Describe Disease Type.

At SEAC 93 (July 2006) the committee discussed the confusion inherent in using the terms “atypical scrapie” and “atypical BSE” regarding the nature of the disease agent involved, and the risk to consumers.

It was noted that it was not for SEAC to determine the nomenclature of TSEs, however it was important that the committee is clear and consistent when discussing these issues, particularly with the public.

SEAC concluded that:

- the term “atypical scrapie” in sheep was not ideal, however as it was in common usage a change in nomenclature now would be confusing.
 - it was important to clarify that, in contrast to classical scrapie, which appears benign, the human health implications of atypical scrapie are not known.
 - the use of the term “atypical BSE” in cattle should be strongly discouraged.
-

BARB cases

At SEAC 88 (June 2005), Defra asked the committee to:

- comment on the findings of two studies comparing the sequences of the prion protein gene (PRNP) carried by BARB cases and healthy control animals, one carried out in Great Britain (GB) and the other in Northern Ireland (NI).

The studies address the issue of possible genetic predisposition to BSE, either spontaneously or by increased susceptibility to exposure from an exogenous source.

The committee considered that:

- there was some accumulating evidence of a linkage between a specific PRNP promoter polymorphism and susceptibility to BSE.
- although the number of BARB cases in these studies is small (n=108), the results indicated that there is no linkage between any PRNP polymorphism and the BARB BSE cases, specifically.
- there is no genetic (or other reason) to suppose that BARB BSE cases are any different from pre-August 1996 cases.
- the origins of infection in BARB cases were unknown. The most likely explanation for the BSE cases born after 1996 was that the cattle were still exposed to BSE contaminated feed. However, alternative sources for the BSE infection were also possible.
- The SEAC ad hoc Epidemiology Subgroup on UK BARB cases had advised on epidemiological work on BARB cases to examine possible causes. The epidemiological work is continuing.

Professor Hill's Independent Review of the cause(s) of BARB cases

Defra had commissioned Professor William Hill (University of Edinburgh) to carry out an independent review into the cause(s) of BARB cases.

At SEAC 88 (June 2005), Professor Hill informed the committee that

- he had assessed alternative hypotheses as to the causative agent of BARBs, and he considered there was no evidence to

suggest that BSE in BARB cases was different to that observed pre 1996.

- he thought it unlikely that the majority of the BARB cases arose spontaneously.
- he could find no evidence to support the idea that genetic variation in cattle had important effects on susceptibility to this disease either by infection or as spontaneous cases. There was no evidence that BARB BSE cases are being transmitted in a different way to previous cases of BSE.
- he had evaluated the epidemiological evidence and found no evidence of maternal or lateral transmission.
- limited infection via environmental or other non-food borne contamination could not be excluded. However, the likelihood was low given current knowledge of the disease in cattle and the absence of other evidence.
- he considered that contamination of feed remained the most likely cause of BARB cases. No other reasonable hypothesis fits the available data. He noted that pairs and triplets of BARB cases were consistent with this view.

The committee:

- welcomed the report and agreed with its main conclusions.
 - recommended relevant research should be maintained to determine if there is more than one cause of BARBs and if the agent causing BARBs is the same as BSE.
 - pointed out that care needed to be taken not to confuse the amount of PrP^{Sc} protein with levels of infectivity because of uncertainty regarding the precise nature of the infectious agent.
 - agreed that research capacity should be maintained to establish the feed-borne cause of BARB cases.
 - agreed that active and passive surveillance should be maintained worldwide to identify any potential strain variation of BSE that might give rise to atypical cases.
-

BARB Case Clusters

At SEAC 90 (November 2005) Defra updated the committee on the BSE cases born after the 1996 reinforced mammalian meat and bone meal ban in the UK.

The committee was informed that:

- approximately 116 BARB cases had been identified in Great Britain up to 22 November 2005 with BARB cases decreasing in successive birth cohorts. The BARB epidemic is unlikely to be sustained by animals born after 31 July 2000
- geographical distribution of BSE cases had moved from the concentration of pre-1996 BSE cases in Eastern England to a more uniform distribution of BARB cases.
- an investigation into one BARB cluster suggested that the use of a feed bin contaminated prior to the 1996 ban was responsible for the cases.
- feed bins could represent a continued source of occasional infection and advice to farmers is being formulated to reduce this risk.

SEAC commented that:

- it encouraging that no other factor, apart from feed contamination, had been identified as a possible cause of BARB cases.
- the study suggested that only a small amount of contaminated feed may be required for infection and that BSE infectivity can survive in the environment for several years.

SAFETY OF ANIMAL BY-PRODUCTS

Use of category 3 animal by-products in fertiliser

At SEAC 87 (April 2005), Defra asked SEAC to consider a release assessment to estimate TSE-related infectivity levels associated with the use of rendered category 3 animal by-products⁷ in fertiliser for non-pasture land.

The committee:

- was content with the approach used and assumptions made in the risk assessment.
- noted that the assessment predicted that TSE infectivity levels on land as a result of the application of fertiliser would be extremely low. However, considered that because of the likely heterogeneous nature of infectivity in fertiliser and the uneven spread of fertiliser, TSE infectivity levels might be higher in some geographical locations than predicted.
- noted that little is known about the persistence of TSE agents in soil. Thus, intra-species recycling of mammalian protein in fertiliser is possible.
- recommended that, although the risks of transmission of TSEs via this route may be very small, a watching brief should be maintained on CWD and BARB cases to assess the possible persistence of the agent in the environment.

Use of Livestock and Crops from Drayton Farm

At SEAC 91 (February 2006) Defra and FSA asked the committee to review the arrangements for disposal of manure, crops and livestock from an experimental farm on which BSE research had been conducted.

⁷ EU legislation classifies animal by-products (ABP) into Category 1 (high risk material from animals with suspected or confirmed TSE), Category 2 (condemned meat from diseased animals) and Category 3 material (fit for human consumption).

Category 3 material may be used as fertiliser, but if it is of mammalian origin, only if reduced to a particle size <50 mm and pressure cooked (>133°C and 3 bar for 20 minutes). Category 3 material may also be used in compost if reduced to <12 mm and heated to 70°C for at least one hour. Appropriately-treated Category 3 ABP may be applied to non-pasture land. Non-pasture land included a period when farmed animals cannot graze.

The VLA outlined the geography and usage of areas of the farm and the arrangements made for treatment and disposal of animal excreta and milk. It was noted that SEAC had previously advised that waste from orally-challenged animals should be incinerated for the first 28 days, thereafter the excreta should be composted for a year and then could be used to fertilise arable land.

SEAC noted that:

- there was no evidence that BSE is transmitted through environmental sources. Therefore healthy animals could be housed in the disinfected buildings which previously housed cattle experimentally infected with BSE and subsequently slaughtered commercially or used for other purposes.
- there is currently no evidence that the crops subsequently grown on the land which received composted excreta from BSE challenged animals pose a significant infectivity risk to humans or animals.

SEAC agreed that:

- the risks from disposal of residual manure from experimental animals would be much less than historic risks of on farm contamination from naturally infected animals at the height of the BSE epidemic.
- there is no evidence to suggest that there is a TSE risk to humans or animals from the unrestricted movement of healthy sheep grazed on the grassland to which manure from non-BSE cattle was applied.

TSEs IN SHEEP

Atypical scrapie

At SEAC 88 (June 2005), the committee was updated on research in progress on cases of scrapie that had given unusual (atypical) results in the diagnostic tests used in active surveillance. Close to 100 atypical scrapie cases had been identified in the UK.

SEAC was informed that a formal definition of atypical scrapie had not been agreed but that the EC Reference Laboratory expert group and EFSA were considering a classification.

The committee:

- noted progress made in sequencing elements of the prion protein gene of atypical scrapie cases and of developments in immunohistochemical methods to detect abnormal prion protein in atypical scrapie samples.
- noted that transmission studies on samples from atypical scrapie were underway.
- agreed that, now that a number of issues around atypical scrapie are becoming clearer, the SEAC Sheep Subgroup should consider the available scientific information in more depth, and new data immediately it becomes available, because of possible implications for the National Scrapie Plan.

SEAC Sheep Subgroup Report

At SEAC 91 (February 2006) the committee reviewed a position statement drafted by the SEAC Sheep Subgroup.

A survey of GB sheep over 18 months old suggested that the prevalence of sheep infected with atypical scrapie is estimated to be around 82 000 sheep compared with around 50 000 sheep infected with classical scrapie. There are clear differences in the genotype distribution of classical and atypical scrapie with the ARR/ARR genotype relatively resistant to classical scrapie but relatively susceptible to atypical scrapie. VRQ/VRQ animals are susceptible to classical scrapie but no natural atypical scrapie infection has yet been detected in sheep of this genotype.

The Subgroup concluded that:

- it is possible, using biochemical tests, to distinguish reliably between experimental BSE in sheep, atypical scrapie and classical scrapie.
- there is currently no evidence of BSE in the UK sheep flock.
- atypical scrapie is experimentally transmissible to mice and sheep, retaining its biochemical characteristics post-transmission.
- atypical scrapie is found independently of classical scrapie in some sheep flocks and goat herds.
- atypical scrapie should be considered as a distinct TSE in small ruminants and not simply a variant of classical scrapie.
- although there is no evidence that atypical scrapie can be transmitted to humans, this possibility cannot be excluded and there is therefore a theoretical risk to human health.
- the new scientific data and identification of atypical scrapie, while of concern, do not justify immediate changes to the NSP. However, it was strongly recommended that the NSP should be kept under continuous review.

SEAC welcomed the progress made so far and agreed with the recommendations for research made. The committee endorsed the SEAC Sheep Subgroup position statement.

Transmission of BSE between sheep in an experimental flock

At SEAC 89 (September 2005) the committee commented on a report⁸ of preliminary findings of natural transmission of BSE between sheep in an experimental flock.

The preliminary results showed that 2 out of 15 lambs born to ewes that had been orally dosed with BSE, had succumbed to BSE. Defra and the FSA asked SEAC to consider preliminary findings from an ongoing study, set up to investigate whether BSE could spread naturally and persist within a sheep flock, and to provide material for other studies.

⁸ Bellworthy *et al.* (2005) Natural transmission of BSE between sheep within an experimental flock. *Vet. Rec.* 157:206.

The committee considered:

- it was important to note that, to date, there has been no finding of naturally occurring BSE in surveillance of the national sheep flock.

SEAC concluded that:

- although these preliminary findings showed that BSE had been transmitted by natural means, this had occurred in an experimental flock under circumstances when opportunities for transmission had been maximised.
- it was not possible to determine, from the information available, the precise route of transmission.
- no change in the BSE signature, as a result of transmission between mother and offspring, was evident from biochemical tests.
- as the experiment was on going, it was premature to determine the possible transmission efficiency of BSE within a flock or whether it was sufficient to sustain an epidemic.
- BSE had not been found in ongoing surveillance for scrapie, and therefore there is no evidence that BSE currently exists in the national sheep flock.

SEAC will consider further findings from the study as they become available.

The National Scrapie Plan (NSP)

SEAC Sheep Subgroup

In March 2004, Defra consulted the SEAC sheep Subgroup following reports that abnormal PrP had been detected in the brains of ARR/ARR sheep, a PrP genotype thought to be naturally resistant to scrapie.

The Subgroup was asked:

- to consider if this development had any implications for the scientific basis of the National Scrapie Plan (NSP).

The Subgroup:

- endorsed its previous opinion of December 2002, that the NSP strategy to increase resistant genotypes and decrease susceptible genotypes remained scientifically justified.
- considered that, although the new evidence suggested that the ARR/ARR genotype may not be completely protective against natural TSE infection, the relative protection, compared to other genotypes, remained very large.
- however, the basis for the strategy should be kept under review in the light of emerging scientific findings with respect to the possible detection of scrapie infections in animals of genotypes currently thought to be most resistant to infection.

In July 2004, the Subgroup was asked:

- to consider four options proposed by Defra for the NSP as part of a wider consultation of stakeholders on future plans for the NSP.

The Subgroup:

- considered that strategies which reduced the prevalence of infection in the national flock most rapidly, were the most desirable.
 - considered that a solution close to the current NSP, with compulsory ram genotyping and removal from use and sale of some scrapie-susceptible genotypes, was the most scientifically desirable.
 - however, recognised that there may be potential practical difficulties with this option. In some cases there were genetic constraints for the sheep industry as well as associated cost issues and therefore the Subgroup recommended that an additional option, a combination of mandatory and voluntary genotyping of certain sheep with removal of some genotypes could also be considered.
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Molecular Evolution of the sheep PRNP, Slate Paper

At SEAC 90 (November 2005) SEAC considered a recent paper on molecular evolution of the sheep prion protein gene (PRNP) by Slate⁹. Using theoretical molecular analyses the author concluded that PRNP in sheep had evolved by balancing selection rather than positive selection to maintain variation in PRNP and include genotypes relatively susceptible to scrapie. This was in contrast to the aim of the NSP which is to selectively breed for genotypes relatively resistant to scrapie.

SEAC noted that:

- if desirable characteristics of sheep were lost by implementation of the NSP, consideration of the relative importance of these characteristics, and of mechanisms to reintroduce these characteristics, would be needed.
- Defra had commissioned a semen bank to preserve existing prion protein gene variation as well as a project to examine the potential relationship between PRNP genotype and fitness and production traits.

SEAC concluded that:

- although the methodology used was sound, the conclusions were not as robust as claimed.
- the paper did not raise any new issues that had not already been considered.
- further and more detailed consideration of these issues would be raised at the forthcoming SEAC sheep subgroup meeting.

⁹ Slate (2005) Molecular evolution of the sheep prion protein gene. Proc. R. Soc. B. 272, 2337-2344.

TSEs IN GOATS

At SEAC 86 (March 2005), following the finding of possible BSE in a UK goat which died in 1990, Defra and FSA asked SEAC:

- for its view on further research and the current level of risk in relation to consumption of UK goat meat or dairy products.

SEAC was presented with experimental evidence about the case.

The committee:

- agreed that the evidence suggested the goat had indeed been infected with BSE.
- noted that the goat had been born around the time of the peak of the BSE epidemic and before the feed bans had been introduced. Therefore, it was likely to have been exposed to feed highly contaminated with the BSE agent.
- noted that BSE had not been found in the offspring of this goat or in other goats from the farm. It therefore appeared to be an isolated case.
- concluded that there is no evidence for BSE in the current UK goat herd, and as goats are no longer exposed to contaminated feed the likelihood of goats in the current flock being infected with BSE is low.
- noted that surveillance of TSEs in goats is very limited and welcomed plans to increase surveillance and to examine other historical samples of goats that may be available, which should enhance confidence in this conclusion.
- concluded that, on the basis of current evidence, and the control measures currently in place aimed at reducing potential risk, it was reasonable for the FSA to continue not to advise against the consumption of goat meat or dairy products.
- considered that, as surveillance is very limited and the distribution of BSE infectivity in goats is not well understood, a potential risk of BSE from goat meat and dairy products could not be entirely excluded.

ANALYTICAL TECHNIQUES ON ABNORMAL PRION PROTEIN

Protein misfolding cyclic amplification (PMCA) tech

At SEAC 89 (September 2005), the committee commented on a report¹⁰ describing the use of an automated protein misfolding cyclic amplification (PMCA) technique to increase the amount of abnormal prion protein in the blood of scrapie affected hamsters to a detectable level was considered. The report showed that after PMCA, PrP^{Sc} had been detected in the blood of 16 out of 18 hamsters showing clinical signs of scrapie.

The committee noted:

- that while the method did not appear to give false positives (PrP^{Sc} was not detected in the blood of any of the non-infected animals) it would be important to examine why PrP^{Sc} was not detected in two of the affected animals since false negative results would invalidate it as a screening test.
- that the amplification phase of the test in the paper took several days to complete and the detection was by Western blot, a relatively insensitive detection method.
- to develop the test further, the time taken for amplification could be shortened, and a more sensitive detection method used.
- that it would be important to see if the method could detect PrP^{Sc} in the blood of pre-symptomatic animals.
- that the amplification step required normal brain tissue from the same species, which may hinder its use to screen human samples.

The committee concluded that:

- this sensitive technique was potentially applicable to detection of abnormal prion protein in the blood of live animals or humans in preclinical stages of infection.
- however, it would require significant further development and evaluation before it could be used routinely.

¹⁰ Castilla *et al.* (2005) Detection of prions in blood. *Nature Medicine* published online 28/08/05.

Conformation-dependent immunoassay (CDI) for abnormal prions

At SEAC 88 (June 2005), SEAC commented on a recent paper¹¹ which had reported that the conformation-dependent immunoassay (CDI) for abnormal prions was more sensitive than other biochemical tests.

The committee:

- commented that, unlike most biochemical tests, it did not rely on proteinase K (PK) digestion of prions and could detect PK sensitive forms of abnormal prions.
- expressed caution about the assumption that the test was capable of measuring the infectious agent, as the form of prion constituting the infectious agent was still unclear.

¹¹ Safar *et al.* (2005) Diagnosis of human prion disease. *Proc. Natl. Acad. Sci. U S A.* 102, 3501-3506.

ANNEX

Minute of the SEAC 90 (November 2005) Q&A session

1. The Chair explained that the purpose of the question and answer session was to give members of the public an opportunity to ask questions related to the work of SEAC. He reminded everyone that the committee's remit is to provide scientific advice on TSEs. The committee does not take risk management or policy decisions on behalf of Government.
2. Mr Graham Steel, co-founder of the CJD Alliance, asked two questions, (i) in relation to the recently published paper by Alvarez *et al.*¹² on the potential of (FLAIR) MRI for detecting CJD before the onset of clinical symptoms - does the committee acknowledge this development of early diagnosis may pave the way when considering issues such as putative treatments? (ii) when considering environmental issues, will SEAC be seeking to establish the outcome of the FatePride study, which is scheduled to conclude on 1st January 2006?
3. A member agreed that it would be very important to be able to diagnose vCJD early, so that if and when there was an effective treatment it could be used as early as possible. It was explained that some clinical cases of CJD show abnormalities on MRI scans and MRI is useful in diagnosing vCJD. Alvarez *et al.* report findings in an 80 year old woman who presented with a subarachnoid haemorrhage and abnormalities on MRI scan. Two years later she was diagnosed with sCJD and had a further scan that also showed abnormalities. The authors suggest that the abnormalities in the first scan were in fact early signs of sCJD. The member said that, in his opinion, the abnormalities seen in the earlier MRI scan were most likely due to the subarachnoid haemorrhage, and that it would be entirely speculative to suggest that they were due to subclinical CJD. He suggested that it was unlikely that MRI would be useful for early pre-clinical diagnosis of CJD as this technique has low sensitivity and specificity, even in clinical cases.
4. A member who was involved in the EU FatePride study explained that biochemists and geochemists were trying to determine the role of environmental factors (e.g. distribution of metals in the soil, presence of organophosphate pesticides) in the development of prion diseases such as BSE, scrapie and CJD. The study was

¹² Alvarez *et al.* (2005) Magnetic resonance imaging findings in pre-clinical Creutzfeldt-Jacob disease. *Intern. J. Neuroscience*, 115:1219-1225.

likely to be extended until mid 2006 and when it was finished, he would report the findings to SEAC.

5. Dr Brian Matthews noted that the available information on the incidence of CJD in various countries, other than the UK, indicates that there is no obvious decline in the numbers of cases being reported. However, in the UK there seems to have been a steady decline in the number of suspected cases, and therefore of confirmed cases, for the past several years. He asked 3 questions: (i) What are the causes of the decline in the number of suspected cases reported in the UK over the past few years? (ii) What is the effect of this decline in reports of suspected cases on the certainty of the decline of the number of new cases of vCJD reported in the UK? (iii) What is the effect of this decline in reports of suspected cases on the certainty that new cases of iatrogenic transmission of CJD and/or vCJD could be identified?
 6. Professor Ironside commented that the number of suspected cases of sCJD reported each year had varied since surveillance began, but numbers had appeared to decline in the past 2 years. However, this was unlikely to be due to significant numbers of cases being missed. As a way of checking to see if cases had been missed, NCJDSU had looked back at diagnosed cases of atypical dementia but had not identified any cases of CJD. The recent decrease in numbers of suspected cases reported was therefore probably due to improvements in clinical diagnostic criteria and the resultant improved quality of referrals. NCJDSU had very good links with clinicians and pathologists across the UK.
 7. Professor Ironside commented that the NCJDSU was involved in the Transfusion Medicine Epidemiology Review study that had led to the identification of the two probable cases of vCJD transmission via blood transfusion and was also involved in the Progressive Intellectual and Neurodegenerative Disease study of neurological disorders in children. While it was impossible to ensure identification of all cases of vCJD, those that were identified were thoroughly investigated to see if they could have been caused by secondary transmission.
 8. The Chair thanked the members of the public for asking these interesting questions.
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Minute of the SEAC 85 (November 2004) Q&A session

1. The Chair invited members of the public who had submitted questions in advance of the meeting to ask their questions and then invited questions from the floor.

Question 1

2. With reference to the case of probable transmission of vCJD via blood transfusion, the committee was asked if there had been any control studies in subjects of a similar age and clinical condition to assess the possible presence of abnormal prion protein in spleen tissue.
3. On behalf of the committee, Professor Ironside explained that this particular patient had been traced through the Transfusion Medicine Epidemiology Review (TMER) study funded by DH. As part of this study, spleen tissue from post mortem of normal controls and patients with other neurological diseases had been performed and in none of these cases was abnormal PrP detected, although the cases were limited in number. Also, no abnormal PrP had been found in other DH-funded studies to examine the brain and other tissues collected from autopsies of elderly and younger individuals.

Question 2

1. In view of recent findings from studies of transgenic mice expressing forms of human prion protein, which suggested BSE infection may be influenced by polymorphisms at codon 129 of PrP gene, the committee was asked for data on the number and genotype of sporadic CJD cases, and if the pattern had changed within the last 15 years.
2. In answer, Professor Ironside presented information on sCJD deaths from 1985 to 29 November 2004 that indicated the number of sCJD deaths per annum in the UK was increasing, but explained that this was possibly due to better case ascertainment, particularly in the elderly. Comparable data have been obtained in European countries and Australia, which showed similar changes in the incidence of sporadic CJD. France, Germany and Italy had higher relative mortality rates for sCJD than the UK, over the period examined (1 Jan 2004 to 30 September 2004).

3. Professor Ironside explained that during the period 1 May 1990 to 29 November 2004 there were 756 sCJD cases (dead and alive), with genotype data available from 476 cases. The codon 129 genotype distribution was 65% MM (310 cases), 17% MV (80 cases) and 18% VV (86 cases).
4. Professor Ironside noted there had been increases in the VV and MV proportion of cases over time but believed this to be largely due to increased surveillance in young patients, presenting with a variety of neurological signs and symptoms, with a higher proportion of VV or MV genotypes. Between 1 May 1990 and 31 Dec 1995, 75% of sCJD deaths were genotype MM (96 cases), 11% were MV (14 cases) and 13% were VV (17 cases). Between 1 Jan 96 and 31 Dec 2003, 62% of sCJD deaths were genotype MM (191 cases), 19% were MV (59 cases) and 19% were VV (58 cases).
5. Professor Ironside commented that in the UK, clinical, biochemical, pathological and genetic analysis was performed for each case of CJD. Additionally, material from many of the cases, particularly from younger patients, had been experimentally transmitted to mice to investigate the possibility that a BSE strain may be responsible for the disease, but so far this had been negative. However, it was not assumed that vCJD would necessarily be the only manifestation of BSE-associated disease in humans, particularly in those people with different genotypes of PrP. However, it was reassuring that the PrP western blot profile of the second blood transfusion-associated case in an individual of the MV genotype was clearly identifiable as vCJD and was similar to that found in MM genotypes.

Question 3

1. The committee was asked when a non-invasive blood test for vCJD would be available for the haemophilia community. The Chair referred to DH for comment.
2. Dr John Stephenson (DH) replied that a diagnostic non-invasive blood test was a research priority for DH. However, no test was currently available. DH was also in liaison with companies working on such tests. Dr Stephenson indicated that Professor Christine Lee at the Royal Free Hospital, London was co-ordinating the surveillance of haemophiliac patients in the UK and could be approached for further details.

Question 4

1. The committee was asked whether the ethical issues had been considered if a blood test for vCJD became available.
2. Dr Stephenson explained that the National Blood Centre was setting up a test assessment facility to prepare the blood services for the introduction of such testing. In addition, DH had asked the Health Protection Agency and the Nuffield Council for Bioethics to set up a workshop to consider the ethical issues of blood testing for vCJD infection.

Question 5

1. The committee was asked if research on immune system reactions, which may be an early marker of TSE disease, was being pursued.
2. Dr Steve Dixon (FSA) explained that the FSA is funding work to search for metabolic biomarkers of TSE infection and to look at the use of erythroid differentiation-related factor (EDRF) as marker of TSE disease. Dr Barrowman indicated that results of a Defra funded metabolomics study of BSE infection at the Institute for Grassland Research may be available later this year. Dr Matthews indicated that an infra red spectroscopy TSE test is being validated by EFSA on post mortem tissue from clinically-affected BSE cases. If successful, the test would be evaluated using samples from animals with preclinical disease.

Question 6

1. In response to a question received in advance of the meeting about the case of possible BSE in a French goat, the Chair explained that this issue had been covered earlier in the meeting, under item 3 (paragraphs 12-14 above).
2. The committee had also been asked by the questioner if it endorsed the 26 November 2004 European Food Safety Authority (EFSA) statement on goat milk¹³. The Chair replied that SEAC had not changed its view that goats milk from healthy animals is unlikely to pose a significant risk to human health, and that therefore the EFSA statement was consistent with previous advice from SEAC.

¹³ Statement of the EFSA Scientific Expert Working Group on BSE/TSE of the Scientific Panel on Biological Hazards on the health risks of the consumption of milk and milk derived products from goats [E F S A | European Food Safety Authority](http://www.efsa.europa.eu)

3. The questioner had also asked whether new EC legislation required that samples from goats and sheep that had tested positive for a TSE be tested by bioassay. Dr Matthews explained that from 31 January 2005 all cases in small ruminants that had initially tested positive would then be tested by discriminatory western blot or ELISA. If an abnormal result was obtained, the samples would be submitted to a ring trial using ELISA, western blot and IHC. Only if the outcome from all these tests was unusual would a bioassay be considered.