

Surveillance of tses in sheep and goat in relation to the risk of infection with bovine spongiform encephalopathy agent and related actions to be taken at EU level

OPINION ON: Actions to be taken on the basis of (1) the September 1998 SSC Opinion on the Risk of infection of sheep and goats with the BSE agent and (2) the April 1999 SEAC Subgroup report on Research and surveillance for TSEs in sheep

ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE AT ITS MEETING OF 27-28 MAY 1999

Preamble:

The Scientific Steering Committee remains preoccupied by the risk that BSE has been introduced in the European sheep and goat flocks, as expressed in its opinion of 24-25 September 1998 on the *Risk of infection of sheep and goats with the BSE agent*.

The present opinion addresses only the aspects of surveillance and related research actions to be taken at EU level. The recommendations made in the opinion of 24-25 September 1998 regarding specified risk materials, monitoring of the evolution in knowledge on infectivity distribution in tissues, the ban on feeding ruminant-derived products to sheep and goats, etc. remain valid.

Regarding the geographical risk assessment in that opinion, the SSC considers as essential and urgent:

1. Assessment, for all EU countries, of the risk that sheep and goats have been fed BSE-contaminated MBM. It is recommended that the European Commission implements the recommendation formulated in section 4 of the SSC's Full Opinion of 24-25 September 1998, regarding the collection of country-specific information on feeding practices of sheep and goats in the various European countries and their history since the '80s.
2. The development of a method for the assessment of the geographical risk of BSE occurring sheep, by an appropriate adaptation of the SSC method for the geographical risk assessment of BSE in cattle by taking into account the recommendations made in sections 3 (parameters defining the risk) of the same opinion. Consideration of definitions of scrapie/TSE-free flocks as well as scrapie-free countries should be established. There is no reason why there cannot be scrapie/TSE-free flocks in scrapie/TSE affected countries. Movement from such flocks should not create a risk.
3. The exploitation of the information and implementation of the method recommended in the above paragraphs 1 and 2.

1. Historic frame and mandate

Following the release in April 1999 of the SEAC Subgroup report on Research and surveillance for TSEs in sheep, the European Commission invited the Scientific Steering Committee « *to provide the Commission with an opinion on whether or not the SEAC report is, in general, in line with the SSC opinion of 24-25 September 1998 on the Risk of infection of sheep and goats with the BSE agent . In addition, the Commission invited the SSC to provide an opinion on whether it is justified to take action as quickly as possible at Community level, and to what extent the SEAC recommendations are applicable to the entire Community*».

At its meeting of 22-23 April 1999, the SSC adopted the following statement:

" Recognising the different mandates that were the basis of the SSC opinion and the SEAC Report, the SSC considers that:

- 1) *Both documents are indeed in line with each other concerning the risk that BSE might have been introduced into sheep and goats and concerning the general recommendations that result from the recognition of this risk.*
- 2) *Whilst the SEAC report emphasises the situation in the UK, a focus should also be developed on other European countries with a population of sheep and/or goats, for example with respect to tracing the history of feeding practices with ruminant MBM.*
- 3) *Discrimination between BSE and scrapie in sheep and goats is a key-question. Surveillance and other efforts (e.g., the development of methods) to identify the presence of BSE in sheep and goats should therefore be initiated as soon as possible.*
- 4) *Along the same lines, an exercise should be conducted to assess the possible geographical risk that BSE has been introduced into sheep. The method to assess the geographical BSE risk in cattle which has been developed by the SSC, could be adapted for that purpose.*
- 5) *The TSE/BSE ad hoc Group is invited to urgently evaluate the SSC and SEAC documents with respect to actions that need to be taken. It should report back to the SSC for an opinion at its meeting of 27-28 May 1999.*

The SSC further invites the various Commission services to evaluate their ongoing research programmes in the light of the research priorities proposed in both documents, and to take appropriate action."

Following the above statement, a Working Group addressed the following two questions:

- a) What are, in the SEAC report, the actions that should be undertaken at the level of the European Union.
- b) What are, in the SSC opinion and in the SEAC Subgroup report, the actions and priorities that are necessary? (including the order of priorities of the actions).

2. Scientific background

2.1. European dimension of the problem.

Sheep and goats have suffered from scrapie for centuries in the EU and world wide but the current distribution and incidence of scrapie is largely unknown due to the inadequacy of the epidemiosurveillance networks in different Member States. Until the beginning of the BSE epidemic in the UK in the 1980s there was no particular concern about the national incidence of scrapie (or other TSEs in sheep). One reason was because it is generally accepted that there was no epidemiological relationship between the occurrence of scrapie in sheep and the incidence of Creutzfeldt-Jakob disease (CJD) in humans over a period of over 250 years. However, attention was drawn by the Scientific Veterinary Committee to the high incidence of familial CJD in the Orava region of Slovakia at a level of about 30 times the normal level of 1 per million adults per year. This form of familial CJD is attributed to mutations in the PrP gene at codon 200. This particular mutation is not fully penetrant and some of the workers in Slovakia have suggested that exposure to sheep scrapie may also be necessary for disease to result. This is partly because scrapie had been identified in sheep in the region following a period since the late XIXth century when scrapie was thought to be absent from the country.

Meanwhile, three major pieces of information changed the approach to TSEs in small ruminants: first that BSE can be experimentally transmitted to sheep and goats after oral challenge with brain material derived from cattle with BSE (Foster *et al.*, 1993), second that the agent strain isolated from these sheep and goats was ~~in~~ biologically indistinguishable from the BSE agent (Bruce *et al.*, 1994) and thirdly that the agent strain isolated from three patients with nv-CJD was also indistinguishable from the BSE agent (Bruce *et al.*, 1997). In the opinion on "The risk of infection of sheep and goats with bovine spongiform encephalopathy agent", adopted by the Scientific Steering Committee at its meeting of 24-25 September 1998 the current risk of BSE being introduced through feeding contaminated MBM and now being present in the national flocks was summarised as follows:

"Although there is currently no evidence to suggest that BSE occurs naturally in sheep and goats under field conditions

the following evidence suggests that the previous or current geographical risks of exposure of sheep and goats to infection can not be excluded and should be investigated under field conditions.

In the light of the incomplete information available, the working group concludes that it can not be excluded that BSE, once introduced, may be maintained and spread in the sheep and goat population by means of horizontal and vertical transmission.

Because it has clearly been demonstrated that BSE can be orally transmitted to certain genotypes of small ruminants, and because it is likely that BSE-contaminated MBM has been fed to some sheep and goats, the Scientific Steering Committee has to assume that BSE could have been introduced into sheep and goat population. Therefore it can not be excluded that the risk could persist, even after an effective implementation of a ruminant feed ban.

On the basis of data on feeding practices, sheep and goats in many countries have probably been exposed to the BSE agent through MBM. It is noted that the feeding practices e.g., the age and extent of MBM feeding of sheep and goats, are different from cattle. These will also vary depending on whether the animals are to be used for meat, wool or dairy purposes.

The Scientific Steering Committee considers that if BSE in sheep and goats exists, the most likely way of introduction has been through MBM. It is possible that the BSE-agent has been maintained, propagated and/or recycled by horizontal and vertical transmission in sheep and goats if the agent behaves like scrapie in these species. Maternal transmission is unproven in goats. Other means of transmission are theoretically possible but regarded as extremely unlikely provided current measures are in place and effectively enforced.

In the context of the geographical risk of BSE in small ruminants, special attention needs to be paid to the genotypes in the sheep population and the possibility of horizontal and maternal transmission of BSE in sheep and goats. No information is currently available but it is noted that study of maternal transmission of experimental BSE in sheep is in progress.

Given the existing uncertainties the SSC concluded that whilst BSE has not been identified in sheep and goats under field conditions, the previous or current geographical risks of BSE existence in sheep and goats can not be excluded."

On the basis of this analysis, it is recommended that a focus on scrapie and other TSE of sheep and goats in all EU Member States is developed. The assessment of the geographical BSE-risk of countries or regions, as adopted by the SSC in its revised opinion of 23 April 1999, could be used as an indicator for the current and near-future risk that sheep and goats could be infected with the BSE agent similar risk factors as for BSE in cattle are involved. Some additional factors to be taken into account for the hypothetical occurrence of BSE in small ruminants, such as the influence of genotype, the higher possibility of maternal and horizontal transmission and selective husbandry practices of those involved in intensive sheep breeding for fattening and milk production.

2.2. Listing of key issues with respect to the risk that BSE might have been introduced into sheep and goats, which seem to emerge from the SSC and/or SEAC reports:

- A sheep experimentally infected orally with 0.5g of infected bovine brain homogenate developed clinical disease at 734 days and was subsequently shown to have BSE infectivity in its brain and spleen, demonstrates that even small amounts of BSE-infected MBM fed to sheep are likely to have presented a risk of BSE infectivity;
- With the evidence for the inclusion of ruminant derived meat-and-bone meal in sheep feeds, it should be assumed that certain sheep flocks in these circumstances were exposed to BSE agent. The infection, if it replicated in a pregnant female, may well be sustained in the sheep flocks by vertical and horizontal transmission. One of the main problems, however, is obtaining data on historical feeding practices in different countries, regions and flocks. The crucial feature is whether or not concentrates have been fed rather than just MBM due to the problems of cross contamination of supposedly MBM-free diets;
- Molecular analysis of ovine prion protein identifies similarities between BSE and an experimental isolate scrapie

CH1641 (Hope *et al*, 1999). After inoculation of this scrapie strain to AA HH or HR QQ "negative" sheep, a C type PrP was reisolated, a similar PrP glycoform type C as after inoculation of the same type of sheep with BSE. This suggests that molecular strain-typing could distinguish the BSE strain from group B strains of scrapie in sheep but, as the frequency of CH1641 or other C-type scrapie isolates is unknown, it may have limited usefulness for positively identifying BSE in the national flocks. Furthermore, since CH1641 pre-dates the outbreak of BSE by 15 years - it was isolated from a natural case of scrapie culled in June 1970 - its biochemical similarity to BSE provides some circumstantial support that BSE could have originated from a C-type sheep scrapie strain.

- In two "positive" line Cheviot sheep orally challenged with BSE, an atypical TSE strain was isolated. One of the explanations could be that indicating that the phenotype of the BSE agent may not be stable on serial passage within sheep (see SSC opinion on BSE in sheep). If this is confirmed, a major problem will arise when strain typing TSE isolates from sheep using the present methodology (which currently involves mice inoculation and western blot analysis);
- The clinical signs of experimental BSE in sheep could differ from the typical clinical signs of scrapie. This could depend on the effect of the different strain of agent and also possibly depending on the genotype of sheep. This is because after experimental inoculation of BSE an atypical wasting syndrome with slight neurological signs was observed in one ewe. This could cause a major problem in the frame of an epidemiosurveillance network based only upon a clinical suspicion after typical scrapie signs. Moreover, it cannot be excluded that a surveillance targeted on scrapie susceptible genotypes of sheep might miss BSE cases in scrapie resistant flocks. Discrimination between natural BSE (if it occurs) and scrapie, not only at the clinical but also the pathological or aetiological level, by a rapid, reliable and cost-effective test is currently not possible and is likely to be a dot on the horizon for some time to come. But it should be underlined that the development of a practical test to distinguish between scrapie and BSE is an absolute priority. This would enable the small ruminant scrapie/BSE situation in the different countries to be assessed and measures to be taken if necessary to avoid economic barriers based only upon hypotheses.
- Scrapie is a concealed or partially concealed disease in most countries in which it occurs and even financial incentives to report may not reveal the full extent of the disease. Anonymous questionnaires could be a more effective means of estimating the true incidence. The conditions and criteria for an adequate TSE surveillance system, once established, could be used to estimate the quality of a given epidemiosurveillance system. One of the key criteria is the permanent and reliable identification of sheep and goats so they can be traced following movement and to identify the parentage of TSE affected animals and their offspring. This is essential to any control programme or any long term epidemiological study. Another key factor is the need for all farm animal veterinarians and farmers throughout the EU to be aware of the disease and its clinical signs. In the absence of adequate monitoring of slaughtered animals and (as far as possible) fallen stock or *in vivo* testing this would contribute to making the epidemiosurveillance more consistent and to reducing the risk of under-reporting of clinically suspect animals.

3. Opinion: proposed actions and order of priority

On the basis of the above report, the SSC adopts the following opinion:

3.1. Need for pro-active actions

One of the lessons learned from the BSE epidemic is that when confronted with a long incubating "new", possibly zoonotic disease, in the absence of reliable data on the historical and present situation, it is essential to protect public health and to retain public confidence in the actions required to do this and in the products consumed or used by the public. One effective way to preserve public confidence and at the same time reduce the real risk, is to act immediately and to be pro-active. Such scenario should also take into account the results of the BSE and scrapie geographical risk analyses of the different countries and include worst case assumptions for the absence of data in this model such as for *PrP* genotype susceptibility, horizontal and maternal transmission.

The absolute priority for this pro-active actions should be focused on putting in place a system for the protection of the public health from the possibility of BSE in sheep and goats, throughout the EU before the hypothetical infection is in

practice proved to occur or is excluded. This could take the form of a risk reduction policy, rather than a risk elimination policy, and might be achieved initially by uniform adoption of Commission Decision 97/534 EC in all Member States. The same emphasis should be given for the control and eradication of scrapie and other TSE in sheep and goats as it has been done for BSE in cattle in several EU countries. There is further an urgent need for the development of tests and regulations ascertaining high quality epidemiosurveillance for TSE in all ruminant species in all European countries.

3.2. Key-issues

The main factors to make progress in defining the real incidence of TSE and the protection of human health are:

- a. The validation of large scale, low cost, specific and sensitive (applicable at least for the 6 last months of the incubation period but preferably as soon after birth as is possible) tests for *post mortem* and *ante mortem* (tonsil, eye lid) TSE detection in small ruminants. The validation procedure is presently being carried out for four BSE tests in cattle, but this should also be rapidly done for sheep TSE testing.
- b. The development of large scale applicable, low cost, specific and sensitive (at least 6 last months of incubation period, but preferably as soon after birth as is possible) tests differentiating scrapie from BSE or scrapie and non-scrapie strains (including BSE and atypical strains).
- c. The definition of the parameters for a high quality epidemiosurveillance network for TSE in small ruminants and implementation of these networks in all EU Member States, taking into account the geographical TSE risk analysis for small ruminants.

3.3. Proposed immediate actions and order of priority/urgency

3.3.1. Surveillance:

- a. Improve, strengthen and accelerate the implementation in all the EU member states an epidemiosurveillance system for TSE in sheep by an awareness programme that should be set up immediately to acquaint all sheep and goat farmers and veterinarians with the clinical signs of scrapie but also focusing on the possible differing symptoms of BSE in sheep.

In regard to awareness of scrapie and TSE in sheep, didactic material (e.g., a video on scrapie), should be made freely available. Furthermore, didactic material of clinical signs of experimental BSE in sheep should be made, for example using a new series of experiments in sheep challenged with the BSE agent at the Neuropathogenesis Unit of Edinburgh. Veterinary neurologists should be trained to study the clinical signs of experimental BSE in sheep and to record the salient features on video-tape. This is urgent, as awareness is the first step in getting to grips with an epidemic of a new disease.

- b. Testing a statistically representative number of sheep for the presence of TSEs, initially using already available tests and, as soon as they become available, the large scale testing methods for PrP^{Sc}. Presently, only screening for TSE can be done, but as soon as possible, differential diagnoses for scrapie and BSE should be carried out.

Another initiative should also be taken at the EU level in order to develop a scientifically justified regulation for the certification of flocks, countries and zone being free of TSEs in sheep. A better definition of the conditions to declare a flock scrapie free should be envisaged, taking into account new test possibilities (large scale testing *post mortem* or tonsil testing, genotyping, *etc*). This should avoid silent or accidental spread of sheep TSE from false officially certified scrapie-free flocks, countries and zones.

3.3.2. Research:

- a. Modelling of BSE in sheep.
- b. Validation of large scale testing methodology for TSE in sheep, first *post mortem*, later *in vivo*.

c. Creating an efficacious information network between research groups to keep all the concerned groups continuously informed on the progress made in the different TSE in sheep experiments.

3.4. Proposed medium- and long-term actions and order of priority/urgency

3.4.1. Improved surveillance:

Full implementation of an epidemiosurveillance system for TSE in small ruminants in all EU member states, of adequate quality and in accordance with the parameters defined under 3.2.c.

3.4.2. Research:

a. Improvement of the methods and speed of large scale applicable differential diagnosis of BSE and scrapie on *post mortem* samples.

b. Development of *in vivo* tests for TSE diagnosis and differential scrapie-BSE diagnosis (on tonsils, third eye lid but ideally on possible disease indicators in blood samples).

4. Other recommendations

a. Maternal and horizontal transmission occurs in scrapie in sheep. It is recommended to investigate whether this occurs with natural BSE infection. If it does not, the hidden epidemic of BSE in sheep (if it exists) is likely to die out once infection via feed is stopped and the infected generation dies out or is killed.

b. Explicit reference is made to the current openings in the 5th Framework Programme for Research and Technological Development. It is recommended that European consortia propose projects in priority fields identified in this opinion.

c. It is recommended to ensure co-operation between the Commission, key members of the appropriate national scientific advisory bodies and key members of the SSC expert group on risks of BSE in sheep and goats. It might be helpful to have a representative from OIE present. The objective of a first meeting would be to determine a clear objective or objectives against a time-scale and to propose the further actions necessary to achieve this objective. It should be reviewed from time to time.

5. References

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