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Evaluation of the application of Sweden to be recognised as having a negligible risk of classical scrapie

European Food Safety Authority

Abstract

Sweden submitted a request to the European Commission to be recognised as a Member State with negligible risk of classical scrapie. EFSA has been asked to assess if Sweden in its application has demonstrated for a period of at least seven years proposed/in the future, that a sufficient number of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm animals, have been tested annually, to provide a 95% level of confidence of detecting classical scrapie if it is present in that population at a prevalence rate exceeding 0.1%. A risk-based approach using scenario-tree modelling with stochastic simulations was applied. There is lack of data on the actual performance of the approved tests in field conditions, especially in sheep. Alternative scenarios were explored extending the range from the sensitivity provided by the past European Union evaluations of screening diagnostic tests to a sensitivity of 50%, consistent with published data obtained under field conditions in infected goat populations. Using data provided by Sweden in its application, the estimated parameters of the scenario-tree model and the range of values of sensitivity, it is concluded that Sweden has tested annually a sufficient number of small ruminants to meet the requirement. Based on the expected number of samples to be tested in 2015 and future years, Sweden would test a sufficient number of animals to meet the requirement if the actual test sensitivity under field conditions was higher than 80%. It is recommended that specific analytical approaches should be agreed upon for use by other MS when preparing their applications for the recognition of the negligible risk of classical scrapie, and that data on the sensitivity of screening diagnostic tests in field conditions should be generated where possible.

Keywords: scrapie, negligible, risk, classical, Sweden, surveillance

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Summary

Since 1 July 2013, Member States (MS) have been able to submit a request to the European Commission (EC) to be recognised as a MS, or zone of a MS, with a negligible risk of classical scrapie (CS). Sweden submitted a request on 22 August 2014 to be recognised as a MS with negligible risk of CS.

The EC requested the technical assistance of EFSA, to assess if Sweden in its application: a) has demonstrated that, for a period of at least seven years, a sufficient number of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm, have been tested annually, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%; b) and will continue to carry out annually a sufficient number of tests of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%, in order to maintain their status.

After further clarification was obtained on the terms of reference of the mandate, a risk-based method using scenario-tree modelling with stochastic simulation in order to account for the variability and uncertainty of the estimated parameters was selected selected to estimate the overall sensitivity of the surveillance system *(SSe)* of Sweden. An Excel-based user-friendly tool designed by EFSA (2012) was used. The Microsoft Excel® add-in tool @Risk 6.2 was used to conduct Monte Carlo simulations.

Two risk categories with two risk groups were selected: not slaughtered for human consumption (NSHC)/slaughtered for human consumption (SHC), and sheep/goats. The estimation of the relative risk for these two risk categories was done by analysing CS surveillance data at MS level between 2002 and 2014. Currently, there are no data to quantify at European Union (EU) level the overall diagnostic sensitivity of the screening diagnostic tests for the detection of CS in small ruminants over 18 months of age under field conditions. The only data available are from the results of the EU evaluations in relation to the diagnostic sensitivity of the tests approved at EU level. The sensitivity of the screening diagnostic tests (rapid tests) under field conditions is considered to be lower than diagnostic sensitivity estimates obtained under laboratory conditions. Given the uncertainty about the sensitivity of the screening diagnostic tests, alternative scenarios were explored extending the range from the sensitivity provided by the EU evaluations to a sensitivity of 50%. This is consistent with published data obtained under field conditions in infected goat populations.

During the period 2008-2014 and using the test sensitivity derived from the EU test evaluation data and alternative scenarios, Sweden has tested annually a sufficient number of ovine and caprine animals over 18 months of age, sourced from the NSHC and SHC, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%.

Based on the expected number of samples to be tested in 2015 and future years, and on the test sensitivity derived from the EU test evaluation data, Sweden would test annually a sufficient number of ovine and caprine animals over 18 months of age, sourced from the NSHC and SHC, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%.

Based on the expected number of samples to be tested in 2015 and future years and on the results of the alternative test sensitivity scenarios, Sweden would test a sufficient number of animals to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1% if the actual test sensitivity under field conditions was higher than 80%.

In 2013 the EC produced guidelines for drafting a dossier for the recognition of a MS or zones of a MS with a negligible risk of CS. It is recommended that this guideline document be amended to include agreed specific methodologies, to be used in the future by other MS when preparing their applications.

The sensitivity of the screening tests in field conditions is a critical parameter when estimating the *SSe*. There is a lack of data on the actual performance of the approved tests in field conditions, especially in sheep. It would be advisable to generate such data.

The parameters used in this assessment are dynamic. Prior to the assessment of any subsequent application, parameters relating to risk factors and test sensitivity should be reviewed and, if necessary, updated.

Table of contents

Abstract 1
Summary 3
1. Introduction 7
1.1. Background and Terms of Reference as provided by the European Commission 7
1.2. Interpretation of the Terms of Reference 8
1.3. Additional information 9
2. Data and Methodologies 9
2.1. Data 9
2.1.1. Population and surveillance data of Sweden 9
2.1.2. EU surveillance data 10
2.1.3. Sensitivity of screening diagnostic tests 10
2.2. Methodology 10
2.2.1. Risk-based surveillance using scenario-tree modelling 10
2.2.2. Estimation of the overall sensitivity of the surveillance system (*SSe*) using scenario-tree modelling 12
3. Results of the assessment 19
4. Conclusions 20
4.1. General considerations 20
4.2. Historical surveillance 21
4.3. Future surveillance 21
5. Recommendations 21
Documentation provided to EFSA 22
References 22
Abbreviations 24
Appendix A – Description of the EU scrapie surveillance data 25
Appendix B – Results of the evaluation of *post-mortem* rapid tests for detection of TSE in small ruminants 26

1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

Since 1 July 2013, according to point 2 of Section A of Chapter A of Annex VIII to Regulation (EC) No 999/2001[1] as amended by Regulation (EU) 630/2013,[2] a Member State (MS) can submit a request to the Commission to be recognised as a MS, or zone of a MS, with a negligible risk of classical scrapie (CS). In this case, the European Commission (EC) should evaluate this request based on the criteria laid down in point 2.1, and, if the evaluation is positive, the negligible risk status may be approved based on a comitology regulatory procedure with scrutiny. The criteria laid down in point 2.1 are based on those mentioned in Article 14.8.3 of the Terrestrial Animal Health Code of the World Organisation for Animal Health (OIE).

According to point 2.1 of Section A, Chapter A, Annex VIII to Regulation (EC) No 999/2001, where a MS considers that its territory or part of its territory poses a negligible risk of CS, it shall submit to the Commission appropriate supporting documentation, setting out in particular that:

a) a risk assessment has been conducted, and it has demonstrated that appropriate measures are currently in place and have been taken for the relevant period of time to manage any risk identified. This risk assessment shall identify all potential factors for CS occurrence and their historic perspective, in particular the:

   (i) importation or introduction of ovine and caprine animals or their semen and embryos potentially infected with CS;

   (ii) extent of knowledge of the population structure and husbandry practices of ovine and caprine animals;

   (iii) feeding practices, including consumption of meat-and-bone meal or greaves derived from ruminants;

   (iv) importation of milk and milk products of ovine and caprine animals origin intended for use in feeding of ovine and caprine animals;

b) for a period of at least seven years, ovine and caprine animals displaying clinical signs compatible with CS have been tested;

c) for a period of at least seven years, a sufficient number of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm, have been tested annually, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1% and no case of CS has been reported during that period;

d) the feeding to ovine and caprine animals of meat-and-bone meal or greaves of ruminant origin has been banned and effectively enforced in the whole MS for a period of at least seven years;

e) introductions from other MS of ovine and caprine animals and semen and embryos thereof are carried out in accordance with point 4.1(b) or point 4.2;

f) introductions from third countries of ovine and caprine animals and semen and embryos thereof are carried out in accordance with Chapter E or Chapter H of Annex IX.

In point 2.2, it is stated that the MS is to notify the Commission of any change in the information submitted according to point 2.1, relating to the disease. The negligible risk status approved in accordance with that point may, in the light of such notification, be withdrawn. This implies that the

[1] Regulation (EC) No 999/2001 of the European Parliament and of the Council of 22 May 2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. OJ L 147, 31.5.2004, p. 1–40.

[2] Commission Regulation (EU) No 630/2013 of 28 June 2013 amending the Annexes to Regulation (EC) No 999/2001 of the European Parliament and of the Council laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. OJ L 179, 29.6.2013, p. 60–83.

number of tests, required for a period of at least seven years according to item (c) of point 2.1, should also be maintained in the future for the CS negligible risk status to be retained.

The minimum requirements of surveillance for scrapie in small ruminants in all MS, laid down in Annex III to Regulation (EC) No 999/2001, and the requirements for the recognition that a MS has a negligible scrapie risk status, laid down in Annex VIII of the same Regulation, are not based on the same assumptions hence compliance with the former does not mean automatic compliance with the latter. For example for a country with a population of 40 000 – 100 000 ewes and lambs put to the ram, according to Annex III it is required to test 500 ovine animals which have died or been killed, but which were not:

- killed in the framework of a disease eradication campaign,
- slaughtered for human consumption.

This sample size of 500 animals will allow the detection of a prevalence of 0.6% with a 95% confidence assuming a random sampling in an infinite sampling population using a perfect test (100% sensitive). However, the declaration of negligible risk of CS requires the testing of sufficient animals to provide a 95% level of confidence of detecting CS if it is present in that population at prevalence rate exceeding 0.1%. Assuming a random sampling in an infinite sampling population using a perfect test (100% sensitive), a minimum of 2 994 animals would need to be tested to meet this criterion, irrespective of species or surveillance streams.

Denmark submitted a request to the EC to be recognised as a MS with negligible risk of CS on 30 August 2013, Finland submitted a similar request on 25 June 2014 and Sweden on 22 August 2014. The EC assessed these applications positively as regards the criteria in item (a), (b), (d), (e) and (f) of point 2.1 of Section A of Chapter A of Annex VIII to Regulation (EC) No 999/2001, but so far did not conclude its assessment as regards item (c).

In the framework of Article 31 of Regulation (EC) No 178/2002,[3] the EC requests the technical assistance of EFSA, to assess if Denmark, Finland and Sweden, in their respective applications:

- have demonstrated that, for a period of at least seven years, a sufficient number of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm, have been tested annually, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0,1%;
- and will continue to carry out annually a sufficient number of tests of ovine and caprine animals over 18 months of age, representative of slaughtered, culled or found dead on farm, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%, in order to maintain their status.

Three different reports, one for each applying MS, are produced by EFSA to answer the Terms of Reference (ToRs) provided by the EC. This report concerns Sweden.

1.2. Interpretation of the Terms of Reference

The following points on the interpretation of the ToRs were clarified with the EC:

- Retrospective analysis of surveillance data is conducted on an annual basis, i.e. estimating the confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1% in each year separately. EFSA has not considered any method that accounts for the cumulative evidence provided by the analysis of historic surveillance data.
- The period for which surveillance data will be analysed retrospectively is 2008–2014.
- The assessment of whether or not the applying MS will continue to carry out a sufficient number of tests will refer to the future in general and not just specifically to 2015, the first year after the retrospective analysis.

[3] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

- Sheep and goats will be considered as a single population (small ruminants) in the assessment. The small ruminant population could be stratified (sheep and goats) in the analysis according to the prevalence observed at national or EU level in each species or any other pre-established criterion.
- The assessment will be conducted using raw data provided by Sweden in the dossier and new data that they may provide upon request. The assessment will also consider other data and information contained in the dossier that may help with the assessment, such as demographic data, organization and implementation of the surveillance system, selection of animals for testing, etc. The aspects of the dossier which are not relevant for the assessment as required in the ToRs will not be considered.
- The EFSA Working Group (WG) producing this assessment will select a methodology that may include a risk-based approach, to be applied across applications.

1.3. Additional information

While reviewing the dossier submitted by Sweden, and in order to implement the analytical approach agreed by the EFSA WG producing this assessment (see Section 2.2), it was considered necessary to request additional data or re-submission of the data already provided in a different format, or at a different resolution level. In particular, the following information was requested:

- Total numbers of sheep and goats (separately) over 18 months of age found dead on farm (fallen stock), by year, during the period 2008–2014.
- Total numbers of sheep and goats (separately) over 18 months of age slaughtered for human consumption, by year, for the period 2008–2014. If not possible, an estimation of the percentage of the total number of adult sheep and goats over 18 months of age found dead/slaughtered for human consumption in Sweden, per year, for the period 2008–2014 would be sufficient, provided that the data for point 1 are made available.
- Total number of adult sheep and goats (separately) in Sweden, by year, for the period 2008–2014.

Sweden submitted the data as requested.

2. Data and Methodologies

2.1. Data

The data needed in the evaluation were determined by the analytical method selected. Once it was agreed to apply scenario tree modelling using stochastic approach, the required data were obtained from different data sources, as explained below.

2.1.1. Population and surveillance data of Sweden

Demographic and surveillance data, including the number of sheep and goats tested for scrapie, test results and future plans for surveillance were obtained from:

- the original application, plus information included in further communications between the EC and the MS;
- additional data provided by Sweden upon request, as described in Section 1.3.

In the paragraphs below, text in italic is quoted verbatim from the reply received by Sweden on future surveillance.

'Active surveillance will focus performed on fallen stock:

- *All sheep and goats above 18 months sent for autopsy.*
- *All fallen goats above 18 months sent for rendering.*
- *A sample of sheep above 18 months sent for rendering, adding up to a minimum of 1500 animals each year.*

In Sweden there is one single organization collecting cadavers for rendering. This company already has a computerized system to register which animals that are collected on the farm and which containers that arrive at the rendering plant that contain animals that should be sampled for TSE. The sampling will be spread over the year with continuous follow up to see that the appropriate volumes of animals are reached. Approximately every 4th animal arriving at rendering will be sampled, and the computerized system will be used as a base to identify which animals that will be sampled.

Future updates of the sampling strategy

Major changes in population size, population structure or import volumes would affect these estimates. Therefore, the surveillance will be continuously updated using the most recent information.'

2.1.2. EU surveillance data

EU surveillance data at MS level have been extracted from the EU Transmissible Spongiform Encephalopathies (TSE) database. Scrapie surveillance data used in the framework of this report are based on the data previously used by the EFSA Panel on Biological Hazards (BIOHAZ, 2014) in a scientific opinion analysing the situation of CS and Atypical scrapie (AS). Such data were provided by the EC, including data reported by MS, and originated from two different datasets, covering the period 2002–2012. Updated data for 2012, 2013 and 2014 were added to compile the most up-to-date dataset containing EU surveillance data (for more details, see Appendix A).

2.1.3. Sensitivity of screening diagnostic tests

Data and information on the performance of screening diagnostic tests approved for the monitoring of TSE in small ruminants in the EU under laboratory conditions have been sourced from the reports of the Institute for Reference Materials and Measurements (IRMM) and EFSA Opinions (EFSA 2005a,b; IRMM, 2005a,b,c, 2010; EFSA BIOHAZ Panel, 2012). These data were produced in the framework of the past EU evaluations of *post-mortem* screening diagnostic tests for the detection of TSE in small ruminants, and are used in the present report as estimates of the diagnostic sensitivity of the EU tests under laboratory conditions (for more details, see Appendix B).

2.2. Methodology

2.2.1. Risk-based surveillance using scenario-tree modelling

For a disease as complex as CS, which is characterised by a long incubation period, the absence of any *in vivo* diagnostic method and the variable susceptibility of individual animals depending on their genetic profile, it is difficult to demonstrate freedom from disease in the territory or part of the territory of an MS. The concept of 'CS-free MS' has therefore been replaced in Annex VIII to Regulation (EC) No 999/2001 by that of 'MS or zone of a MS with a negligible risk of CS' by Commission Regulation (EU) No 630/2013.

Commission Regulation (EU) No 630/2013 amending Annex VIII of Regulation (EC) No 999/2001 also aligned the criteria for a MS to be recognised as having a 'negligible risk of CS' with those laid down in Article 14.8.3 of the OIE Terrestrial Animal Health code for 'scrapie-free country or zone'.[4]

ToR1 of the mandate for the present report refers to a surveillance strategy that must comply with the concept of 'freedom from disease', i.e. the situations in which the monitoring activity is carried out to detect or exclude the occurrence or recurrence or emergence of a disease (Doherr and Audigé, 2001).

Owing to the constraints of the nature of the disease, the application of sampling strategies and the limitations of diagnostic test performance, it is virtually impossible to achieve absolute proof of freedom from disease. Thus, a probabilistic approach is used based on the accumulation of evidence (Cameron, 2012). The implication of such a strategy is that the level of confidence that an animal population is 'free' from disease is proportional to (FAO, 2014):

[4] Available at: www.oie.int.

- the sample size, i.e. the number of animals sampled; the larger the number of animals submitted to testing, the larger is the likelihood of detecting the disease.
- the design prevalence *(DP)*, i.e. the assumed prevalence of disease if it is present and also the probability of infection for each animal in the population; the lower the *DP* is, the larger will be the effort needed to detect the disease. In ToR1 it is 0.1%.
- the accuracy of the diagnostic test in terms of sensitivity and specificity. Sensitivity is a key factor in terms of both sensitivity of the screening test and sensitivity of the surveillance system, i.e. the probability that the surveillance system would detect disease if it were present. Therefore, maximising the sensitivity strengthens the confidence in freedom, reducing the uncertainty when communicating results. On the other hand, specificity is not a problem when trying to substantiate freedom from disease (Martin et al., 2007). Even if potential false positives can compromise the freedom statement, each initially positive animal should be subject to further confirmatory testing. As highlighted in a recent EFSA Technical Report, each surveillance system should encompass all the necessary follow-up testing to resolve potential false positive results (EFSA, 2012).

A surveillance system can be thought of as a type of diagnostic test on the entire population: the population does have or does not have a disease, and the surveillance is applied in order to make a decision on the disease status. The ability of a surveillance system to correctly identify a diseased population is analogous to the ability of a diagnostic test to identify a diseased animal (Cameron, 2009). It is measured quantitatively by the sensitivity of the surveillance system, i.e. the level of confidence of detecting the disease mentioned in ToR1.

As discussed in Stärk et al. (2006), it had been argued by Martin and Cameron (2003) that the assumption in traditional surveillance that the probability of disease is constant across all individuals in the reference population is not realistic. A single standard value for the *DP* would imply that all animals in the population have, on average, the same probability of being infected. This is never true: animals vary in their probability of becoming infected, depending on the nature of the disease and on their susceptibility to it. To deal efficiently with such a context, the evaluation of surveillance systems can be achieved using scenario trees similar to decision tree structures.

The scenario tree is a modelling format for analysis of surveillance systems under a null hypothesis of the country being infected at a level equal to or higher than the specified prevalence. A scenario tree is developed to represent all known significant factors influencing the probability that a unit in an infected population will be detected as infected. The conditional probabilities associated with each branch of the tree are then multiplied together to give the overall probability of each branch outcome, and these are added up for all branches with positive outcomes to give the probability of the whole surveillance process having a positive outcome for a randomly chosen population unit, given that infection is present in the country. The infection and detection nodes of their trees represent factors affecting the probability of disease occurrence in sub-populations that may be targeted by surveillance.

Scenario trees allow the evaluation of the contribution of risk-based surveillance that aims to take into account the differences in risk among animals in the population. In particular, by selecting animals with a higher probability of being infected or a higher probability of being detected if they are infected, the sensitivity of the surveillance can be increased without increasing the total number of animals being tested (Cameron, 2009). If surveillance is targeted towards a group of animals that are at higher risk of being infected, a scenario tree allows us to calculate the sensitivity that we achieve for that particular group. For details of the calculation of the sensitivity of the surveillance system, see Section 2.2.2.

In order to conduct the estimation of the sensitivity of the surveillance system using scenario tree modelling, a tailor-made modification of the risk-based estimate of system sensitivity tool (RiBESS) (EFSA, 2012)has been used. The RiBESS is an Excel-based user-friendly tool designed to calculate the sensitivity of a surveillance system using a risk-based approach according to the formulae described in Section 2.2.2. The Microsoft Excel® add-in tool @Risk 6.2[5] was used to conduct Monte Carlo

[5] Copyright © 2015, Palisade Corporation, NY, USA.

simulations. Ten thousand iterations were used for each simulation performed, which ensured convergence of the model.

2.2.2. Estimation of the overall sensitivity of the surveillance system (*SSe*) using scenario-tree modelling

Scenario tree modelling effectively divides the population into different risk groups based on known risk indicator(s). By applying relative risk of infection in each of these groups, the *DP*, i.e. the theoretical overall probability that a random unit is infected is adjusted in order to estimate the group-level probability of infection, i.e. the 'actual' probability that a random unit from a specific group is infected, based on the available data on the relative risk for the risk indicator/s.

To summarise, a scenario tree is a tool to assist in the calculation of the sensitivity of a component of a surveillance system (Cameron, 2009). In contrast to the simple analysis of representative surveys, the purpose of a scenario tree is to take into account the fact that not all animals in the population:

- have the same probability of being infected (some are at greater risk than others);
- have the same probability of being detected (the sensitivity of detection is greater in some animals than others).

Once the risk indicators are identified and the associated risk parameters estimated, it is possible to combine the different levels in order to obtain the risk groups. If two risk indicators are identified with two levels (categories) each, the four different risk groups can be obtained.

Table 1 below shows the distribution of risk groups in the case of two risk indicators with two categories each.

Table 1: Theoretical distribution of risk groups using two risk indicators with two categories each

Risk indicator I	**Risk indicator II**	
	RI_IIa	**RI_IIb**
RI_Ia	Group:1 $CombRP_1$ $PopProp_1$	Group:2 $CombRP_2$ $PopProp_2$
RI_Ib	Group:3 $CombRP_3$ $PopProp_3$	Group:4 $CombRP_4$ $PopProp_4$

For each risk group, the weighted risk (WR_i) is calculated as follows:

$$WR_i = \frac{CombRP_i}{\sum_{i=1}^{r}(PopProp_i \cdot CombRP_i)} \quad (1)$$

where $CombRP_i$, is the risk parameter for the i^{th} specific risk group (combination of the two risk indicators), $PopProp_i$ is the fraction of the total population allocated in the i^{th} specific risk group and r is the total number of risk groups, i.e. four in the example.

Using WR_i, it is then possible to calculate the effective probability of infection for each risk group i (EPI_i) as follows:

$$EPI_i = DP \cdot WR_i \quad (2)$$

where DP is the overall design prevalence and WR_i is the weighted risk for each group.

Once the EPI_i values are estimated, they can be used as a better estimate **at group level** in order to calculate:

- the **sample size required** in each group in order to have a probability of detecting at least one positive animal, should the actual prevalence be above the EPI_i; or
- the **sensitivity of a round of testing** (*RSe*), i.e. the probability that at least one animal out of the tested animals will return a positive result, should the actual prevalence be above the EPI_i at group level.

The *RSe* is calculated for a finite population as follows:

$$RSe = 1 - \left(1 - \frac{n \cdot TSe}{N - 0.5 \cdot (N \cdot DP \cdot TSe - 1)}\right)^{N \cdot DP} \quad (3)$$

where *n* is the sample size, *DP* is the design prevalence, *TSe* is the sensitivity of the test and *N* is the total population size. The group sensitivity for group *i* (GSe_i) can be calculated for each group just by substituting *DP* for EPI_i, with n_i, being the sample size in each risk group and N_i the total population in each risk group:

$$GSe_i = 1 - \left(1 - \frac{n_i \cdot TSe}{N_i - 0.5 \cdot (N_i \cdot EPI_i \cdot TSe - 1)}\right)^{N_i \cdot EPI_i} \quad (4)$$

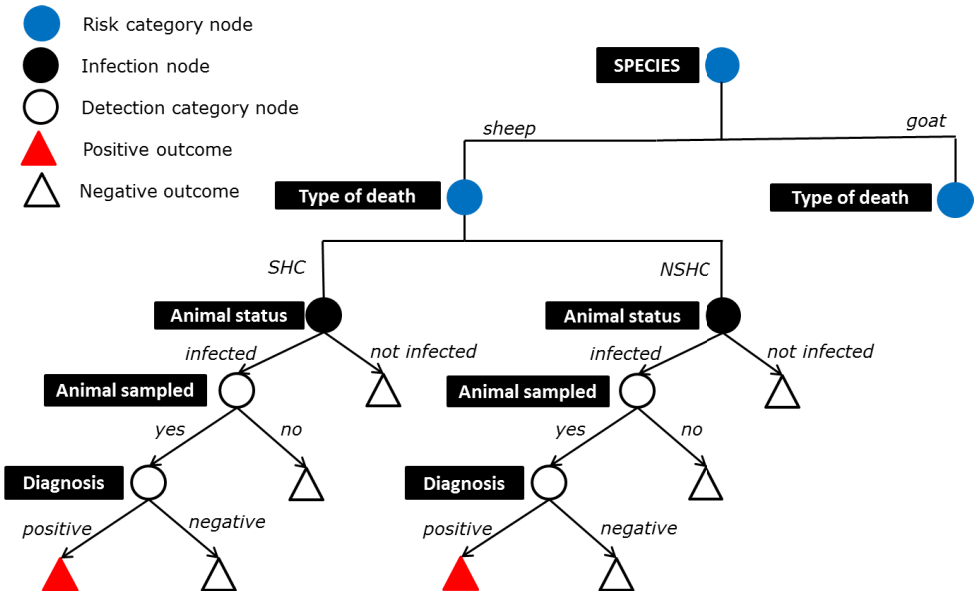
It is now possible to estimate the overall sensitivity of the surveillance system (SSe) as follows:

$$SSe = 1 - \prod_{i=1}^{r} (1 - GSe_i) \quad (5)$$

where *SSe* is the system (overall) sensitivity, GSe_i is the group sensitivity of each risk group and *r* is the number of risk groups included in the survey. *SSe* represents the 'confidence' of detecting the disease given *DP*, *TSe*, *N* and *n*. The *SSe* level required by the legislation is usually 95%.

Input parameters for the calculation of the overall sensitivity of the surveillance system (*SSe*) using scenario tree modelling

The methodology described above has been applied for the calculation of the annual *SSe* to detect scrapie at the designed prevalence of 0.1%. Two risk indicators have been selected: surveillance stream with two risk categories (NSHC, SHC), and species with two risk categories (sheep, goats), as displayed in Figure 1.



Only the sheep section is shown. The same tree applies to the goat section.

Figure 1: Scenario tree flow diagram of the analysis of the active surveillance system for CS

For the calculation of the *SSe* two different categories of parameters are used: those common to all MS and MS-specific parameters.

Parameters common to all MS:

Design prevalence (DP): 0.1%.

Fixed according to the EU legislation.

Sensitivity of the screening diagnostic tests (rapid tests) (TSe)

Various prion protein (PrP) detection methods can be applied in the context of statutory surveillance (enzyme-linked immunosorbent assay, Western blot, immunohistochemistry), but active surveillance screening in the EU requires that the method used must be listed in Regulation (EC) No 999/2001.

Initially, evaluation exercises were carried out using brain tissue from clinical cases of bovine spongiform encephalopathy (BSE) in cattle, and tests performing satisfactorily on bovine tissues were provisionally approved for small ruminants and used for surveillance of TSE in sheep and goats (Commission Decision 2000/374/EC;[6] Regulation (EC) No 1053/2003[7]). In 2003, the EC launched a new evaluation of diagnostic and analytical sensitivity, diagnostic specificity and repeatability of *post-mortem* screening diagnostic tests for TSE using natural CS samples. Based on the results of these evaluations (EFSA, 2005a,b; IRMM, 2005a,b,c, 2010), *post-mortem* screening diagnostic tests were specifically approved for the detection of TSE in small ruminants (Regulation (EC) No 253/2006[8]). Further modifications were made in 2008 and 2009, owing to the withdrawal from the market of some tests, and then in 2010 (Regulation (EC) No 956/2010[9]), with some tests being delisted for performing poorly with regard to AS. The approved test list has remained stable since 2010, with the addition of one new test in 2012 as a result of a new EU evaluation procedure that started in 2008.

IRMM and EFSA published reports summarising the results of the 2003 and 2008 evaluations of the *post-mortem* screening diagnostic tests for the detection of TSE in small ruminants (EFSA, 2005a,b; IRMM, 2005a,b,c, 2010; EFSA BIOHAZ Panel, 2012). When reviewing the results of the evaluations in relation to the diagnostic sensitivity of the tests recommended for approval and used, at least for some years in MS, the lowest reported value for diagnostic sensitivity was 99.6% (95% confidence interval (CI) 98.10–99.99%), based on an evaluation on 246 positive brainstem samples. (Appendix B).

Additional requirements apply to approved screening diagnostic tests in terms of analytical sensitivity. All tests are required to fall within an analytical sensitivity of a maximal 2 $\log_{10}$ inferiority of the most sensitive test. Despite the potential for apparent differences in analytical sensitivity, the EFSA BIOHAZ Panel (2009) concluded that '*no potential differences in field detection performance can be inferred on the sole basis of the difference in analytical sensitivity reported*'.

In practice, a number of factors other than the diagnostic sensitivity of a test under laboratory conditions affect the ability of the test to correctly identify sheep and goats affected by CS, and are discussed below. These factors are difficult to quantify. They contribute to the uncertainty around the value of the parameter for the sensitivity of the test under field conditions and should be taken into account.

[6] Commission Decision 2000/374/EC of 27 December 2000 prohibiting the use of certain animal by-products in animal feed. OJ L 6, 11.1.201, p. 16–17.
[7] Regulation (EC) No 1053/2003 of 19 June 2003 amending Regulation (EC) No 999/2001 of the European Parliament and of the Council as regards rapid tests. OJ L 152, 20.6.203, p. 8–9.
[8] Regulation (EC) No 253/2006 of 14 February 2006 amending Regulation (EC) No 999/2001 of the European Parliament and of the Council as regards rapid tests and measures for the eradication of TSEs in ovine and caprine animals. OJ L 44, 15.02.2006, p. 9–12.
[9] Regulation (EC) No 956/2010 of 22 October 2010 amending Annex X to Regulation (EC) No 999/2001 of the European Parliament and of the Council as regards the list of rapid tests. OJ L 279, 23.10.2010, p. 10–12.

While testing laboratories are kept 'under control' by the regulatory requirement to apply tests within recognised quality systems (ISO, 2005) or equivalent (Regulation (EC) No 882/2004[10])), the initial selection of animals and sampling of material falls largely out of this procedural control.

Regardless of the analytical sensitivity and diagnostic sensitivity of the test used, sample location is key to good sensitivity of the test under field conditions. Current active surveillance screening looks for evidence of accumulation in the brainstem of the abnormal form (PrP^{Sc}) of the cellular PrP (PrP^{c}).

Most of the published data related to PrP^{Sc} dissemination dynamics in sheep naturally affected with CS were obtained in sheep bearing the VRQ/VRQ genotype (for details see EFSA BIOHAZ Panel, 2010). In these animals, lymphoreticular system (LRS) involvement starts in the gut in the first months post exposure, and thereafter spreads to all lymph nodes, reaching a plateau around six months post infection. It is not until an age of between 7 months and 10 months that PrP^{Sc} becomes detectable in the central nervous system (CNS) (brain and spinal cord), where it accumulates following exponential kinetics. There is a paucity of relevant data related to CS dissemination in sheep of other genotypes. However, the data that do exist indicate that in other genotypes the dissemination kinetics of the PrP^{Sc} is slower, and in some cases there is also no LRS involvement (EFSA BIOHAZ Panel, 2010, 2014). Any brainstem samples from animals infected for less than a year are therefore likely to test negative. However, this should not affect the overall sensitivity of the diagnostic test in VRQ/VRQ animals since the minimum age for testing is 18 months of age, if it is assumed that infection occurs at or shortly after birth.

In the case of infected animals over 18 months of age, the combination of the choice of tissue sampled, genotype, age at testing and the accuracy of sampling will all have an effect on the ability of the screening test to detect an infected animal under field conditions. Consistent and accurate sampling of target areas is essential to give confidence in a negative biochemical result. The accuracy of sampling is also critical in the brainstem, as in the brainstem PrP^{Sc} is initially localised to the dorsal nucleus of the vagus nerve, before becoming more widely disseminated as infected animals develop clinical disease (Ryder et al., 2001, 2009; Sisó et al., 2010). Moving away from the target areas at the obex in cattle has also been resulted in a drop in detectable PrP^{Sc} (by a factor of 3 over 6 mm), potentially compromising detection (Moynagh et al., 1999).

Although the impact of this initially localised PrP^{Sc} deposition on test sensitivity in pre-clinical populations under field conditions has not been systematically assessed in sheep, there are several reports of studies in which whole goat herds have been culled and test performance compared. These all concur that, when PrP^{Sc} accumulation within the brainstem is restricted, sensitivity under field conditions is compromised, with different estimates reported in the literature: 47% (Corbière et al., 2013), 53% (Gonzalez et al., 2010) and 64% (Ortiz-Pelaez et al., 2014).

Under field conditions, the sensitivity of a test is likely to be lower than diagnostic sensitivity estimates obtained under laboratory conditions. Currently, there are no data to quantify at EU level the overall diagnostic sensitivity of screening diagnostic tests for the detection of CS in small ruminants above 18 months of age under field conditions.

Given the above, the following approach is used for the parameterisation of the diagnostic test sensitivity *TSe*:

- From the results of the past EU evaluations of screening diagnostic, the lowest value of diagnostic sensitivity obtained with the tests evaluated was selected as the worst case and applied to each MS. A beta distribution was built using 245 successes out of 246 trials (Figure 2).
- Alternative scenarios using different sensitivity values of the screening diagnostic tests were applied, as follows: 90%, 80%, 70%, 60% and 50%.

[10] Regulation (EC) No 882/2004 of the European Parliament and of the Council of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules. OJ L 165, 30.4.2004, p. 1–141.

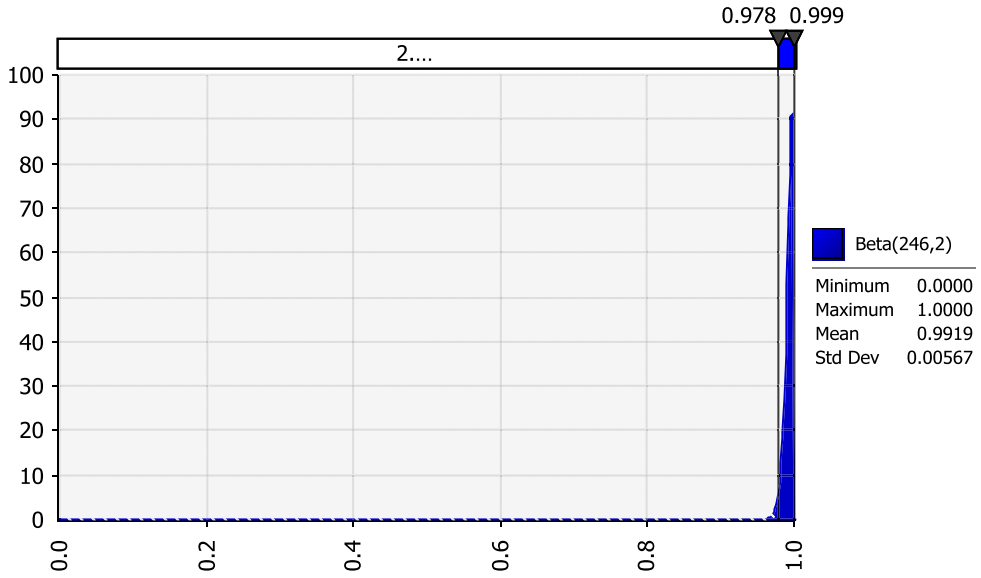


Figure 2: Probability distribution of the sensitivity of the diagnostic test using the results of the EU evaluation reports

Relative risk by surveillance stream (CombRP$_i$)

This risk indicator contains two risk categories, namely, not slaughtered for human consumption (NSHC)/slaughtered for human consumption (SHC) (healthy slaughter and culled).

A preliminary estimation of the specific prevalence of CS by country, year, species and stream has been obtained using the data described in Appendix A.

The excess probability (relative risk) of detecting scrapie in the NSHC stream compared with the SHC stream was based on the calculation of the prevalence ratio (PR), i.e. the ratio of the prevalence observed in the first group to that in the second declared as baseline.

Annual data for each country were used as the unit of analysis. A further restriction was applied, excluding country- and year-specific data when the total number of tested animals in a particular country and year was less than 385, to prevent the possibility that sampling errors > 5% might affect the prevalence estimates used in each calculation.

The estimation of the relative risk NSHC/SHC was conducted by fitting a multi-level negative binomial regression.

The outcome of interest was the number of cases of CS reported by each country in the frame of active surveillance, whereas the total annual number of tested animals was used as an offset of the model. The following independent variables have been included in the model: country, species, year and surveillance stream. Country was included as a random effect. The exponentiated coefficient of the final model represents the PR of detecting CS in the NSHC compared with the baseline category (SHC), taking into account the effect of country, species and year for the entire EU, for the period 2002–2014, under the testing conditions applied by each country in compliance with the EU legislation.

The results of the final model included 262 observations and showed a risk 3.7 times higher (expressed as prevalence rate ratio) (95% CI 2.9–4.6) in the NSHC stream than in the SHC stream.

Therefore, in summary,

- the coefficient and associated standard error of the variable 'surveillance stream' in the final multilevel negative binomial regression model were respectively, 1.297 and 0.112. The corresponding PR was 3.7 (95% CI 2.9–4.6). A normal distribution matching the results obtained with the multilevel negative binomial regression model was used, i.e.

  $\alpha_{NSHC/SHC} = exp$ (RiskNormal(1.297,0.112))

- The resulting distribution (Figure 3) matched the results obtained with the multilevel negative binomial regression model i.e. a risk 3.7 times higher in the NSHC stream than in the SHC stream, with a 2.5% probability of values < 2.9 and a 2.5% probability of values > 4.6.

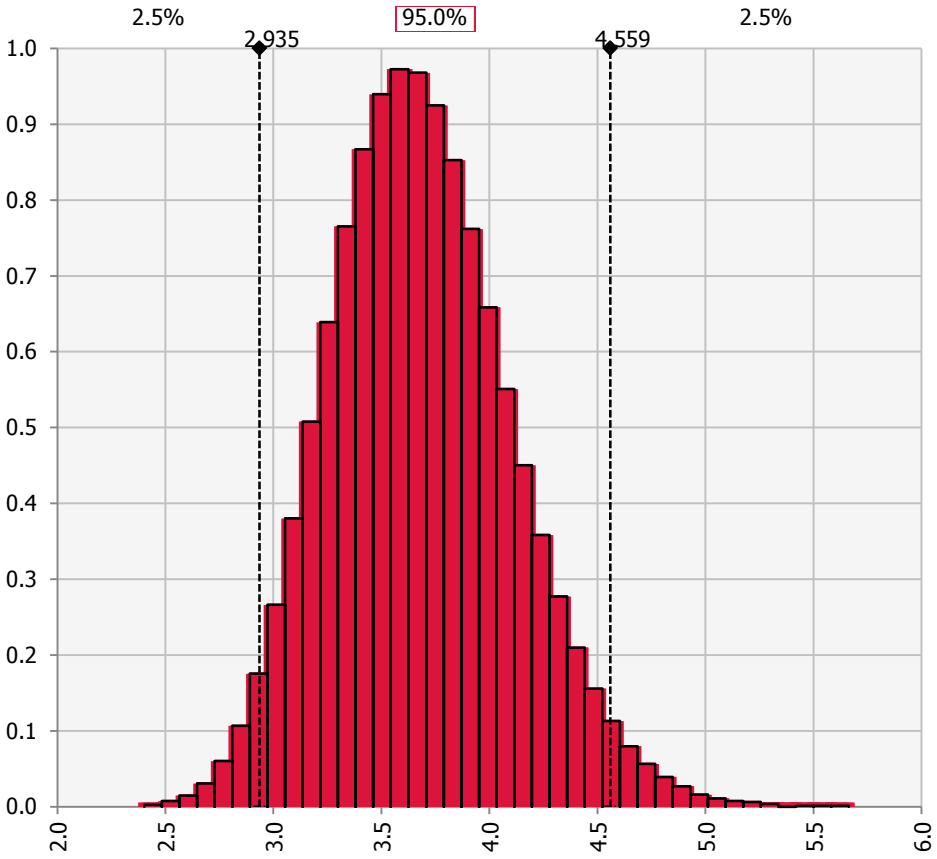


Figure 3: Probability distribution of the relative risk NSHC/SHC

Relative risk by species (CombRP$_i$)

This risk indicator contains two risk categories, namely, sheep/goats.

A similar approach was used to calculate the excess probability (relative risk) of detecting scrapie in sheep compared with goats. It was based on the calculation of the PR i.e. the ratio of the prevalence observed in sheep to that in goats. The estimation of the relative risk sheep/goats was extracted from the multilevel negative binomial regression model fitted to determine the relative risk NSHC/SHC, in which species was included as independent variable.

The results of the final model included 262 observations and showed a risk 2.6 times higher (95% CI 1.9–3.7) in sheep than in goats.

Therefore, in summary,

- the coefficient and associated standard error of the variable 'species' in the final multilevel negative binomial regression model were respectively, 0.9636 and 0.17. The corresponding PR was 2.6 (95% CI 1.9–3.7). A normal distribution matching the results obtained with the multilevel negative binomial regression model was used.

  $\beta_{Sheep/Goat}$= *exp* (RiskNormal(0.9636,0.17))

- The resulting distribution (Figure 4) matched the results obtained with the multilevel negative binomial regression model i.e. a risk 2.6 times higher in sheep than in goats with a 2.5% probability for values < 1.9 and a 2.5% probability for values > 3.7.

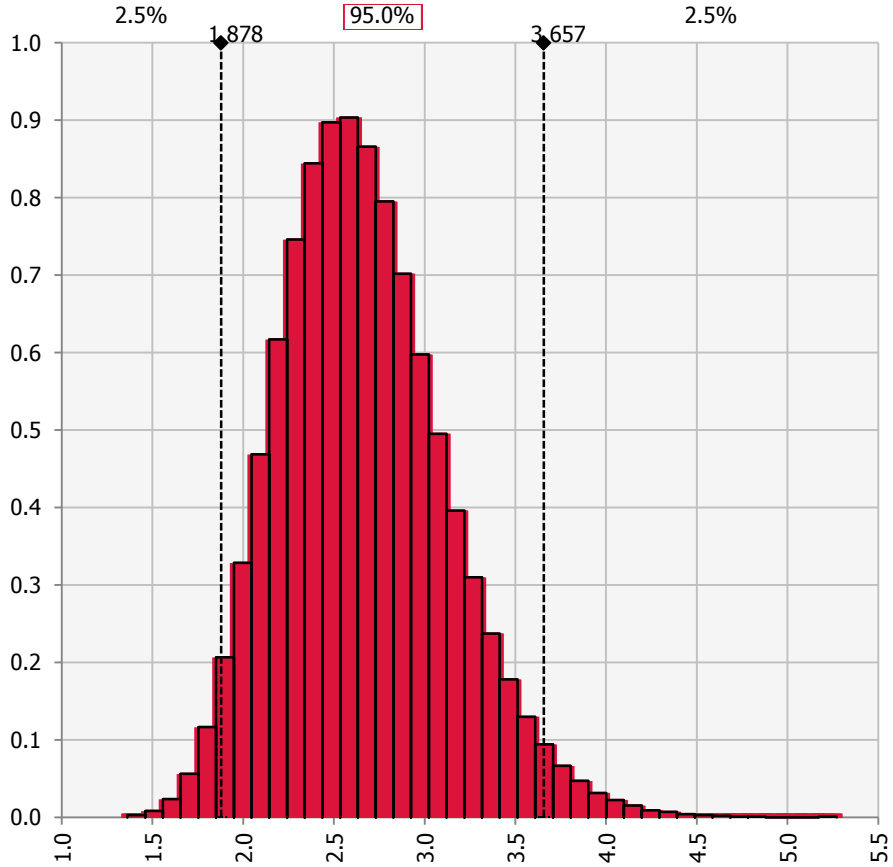


Figure 4: Probability distribution of the relative risk sheep/goats

Country-specific parameters for each MS

The model described in Section 2.2.2 is parameterised for each year under consideration, i.e. 2008–2014 and also for future years.

Sheep and goat populations within each surveillance stream (N_i)

The population of sheep and goats will vary between years. The differences in the sheep and goat populations within each surveillance stream are taken into account in the model described in Section 2.2.2. Using the notation described earlier,

N_1=Total NSHC sheep per year

N_2=Total SHC sheep per year

N_3=Total NSHC goats per year

N_4=Total SHC goats per year

$N = \sum_{i=1}^{r} N_i$= Total population of sheep and goats per year.

The values for N_i used in the analysis are provided in Table 2.

Number of sheep and goats tested within each surveillance stream (n_i)

Finally, the number of sheep and goats tested within each surveillance stream (NSHC, SHC) are defined as:

n_1 =number of NSHC sheep tested per year

n_2 =number of SHC sheep tested per year

n_3 =number of NSHC goats tested per year

n_4 =number of SHC goats tested per year

The values for n_i used in the analysis are provided in Table 2.

Assuming the sheep and goat population in the NSHC and SHC streams reported for 2014, and based on the details of the plans for future testing as part of the active surveillance programme of scrapie for small ruminants in Sweden as described in Section 2.1.1, the expected numbers of samples to be tested, by species and surveillance stream, are (included in Table 2):

Sheep: 1 500 NSHC

Goats: as in 2014: 153 NSHC

Total expected number sheep and goats tested: 1 653

Table 2: Sweden. Summary of test and population data by surveillance stream (2008–2014) and expected number of sheep and goats to be tested annually in the future

Year	Total NSHC sheep (N_1)	Total NSHC sheep tested (n_1)	Total SHC sheep (N_2)	Total SHC sheep tested (n_2)	Total NSHC goats (N_3)	Total NSHC goats tested(n_3)	Total SHC goats (N_4)	Total SHC goats tested (n_4)
2008	7 400	3 825	31 928	9	170	51	319	3
2009	7 450	4 804	33 793	1	180	54	341	0
2010	8 000	6 499	32 724	0	190	27	264	1
2011	8 700	6 965	33 056	115	220	19	247	0
2012	8 700	7 316	34 846	87	240	26	587	0
2013	8 400	7 470	34 675	9	250	19	473	0
2014	8 400	5 805	34 029	28	230	153	457	0
Future	8 400	1 500	34 029	0	230	153	457	0

Summary of the distribution of risk groups using two indicators for the estimation of SSe *for CS*

Table 3 presents the parameterisation of Table 1 for the estimation of *SSe* for CS each year. The parameter estimates described above can be inserted into Table 3 and then subsequently in equations (1), (2), (4) and (5).

Table 3: Actual distribution of risk groups using two risk indicators with two categories each and associated relative risks for classical scrapie according to the model

Risk indicator I	Risk indicator II	
	NSHC	**SHC**
Sheep	$CombRP_1 = \alpha \times \beta$ $\mathrm{PopProp}_1 = N_1/N$	$CombRP_2 = \alpha$ $\mathrm{PopProp}_2 = N_2/N$
Goats	$CombRP_3 = \beta$ $\mathrm{PopProp}_3 = N_3/N$	$CombRP_4 = 1$ $\mathrm{PopProp}_4 = N_4/N$

3. Results of the assessment

The summary of the estimation of the overall sensitivity of the surveillance system (i.e. the level of confidence of disease detection mentioned in the ToR) in Sweden for the different scenarios using historical and future surveillance data is shown in Table 4.

Table 4: Sweden. Results of the estimation of the Sensitivity of the surveillance system *(SSe)* (corresponding to the % level of confidence of disease detection) expressed as the 5th percentile of the output probability distribution, for the period 2008–2014 and future surveillance using the different values of sensitivity.

Year	EU evaluation	90%	80%	70%	60%	50%
2008	1	1	0.9998	0.9994	0.9978	0.9927
2009	1	1	1	1	0.9997	0.9985
2010	1	1	1	1	1	0.9999
2011	1	1	1	1	1	0.9999
2012	1	1	1	1	1	1
2013	1	1	1	1	1	1
2014	1	1	1	1	1	0.9996
Future	0.9773	0.9664	0.9490[(a)]	0.9237[(a)]	0.8867[(a)]	0.8339[(a)]

(a): Values lower than 0.95.

4. Conclusions

4.1. General considerations

- The variability and uncertainties about the key parameters for the assessment (i.e. the relative risks of sheep versus goats and of NSHC versus SHC and the sensitivity of the screening diagnostic tests) have been addressed by applying probability distributions to be used in the context of a stochastic approach in order to estimate the overall sensitivity of the surveillance system.
- It is acknowledged that different analytical approaches may produce different results. The application of representative versus risk-based approaches, annual versus cumulative analysis of historic surveillance data, or deterministic versus stochastic, requires the use of different input parameters and assumptions specific for each.
- The purpose of this report is to apply an epidemiologically sound methodology in a transparent manner so that repeatable results can be produced when applying the same method/s and data. The parameterization of variables of the models has been explained and justified accordingly.
- The EFSA Working Group producing this assessment felt that the existing laboratory data on the sensitivity of the screening diagnostic tests from past EU test evaluations were not representative of the sensitivity under field conditions, and may result in an overestimation of the surveillance sensitivity.
- Given the uncertainty about the sensitivity of the screening diagnostic tests, alternative scenarios were explored extending the range of values from the sensitivity provided by the EU evaluations to a sensitivity of 50%, consistent with published data obtained under field conditions in infected goat populations.
- The calculations of the sensitivity of the surveillance system (i.e. the level of confidence of disease detection mentioned in the ToR have been done based on the assumption that the animals tested are representative of the populations from which the sample was drawn. The assessment of whether this assumption is tenable is beyond the scope of the ToR of this mandate.
- In the analysis of future surveillance it has been assumed that the number of small ruminants tested will be as declared by Sweden in the dossier or in further communications. If the actual number of tests were different, the results of the analysis with regard to future surveillance

would not be valid and should be re-calculated. Equally, if it was decided to apply an alternative methodology to the same data, the results may be different.

- The regulatory requirements for active surveillance for scrapie in small ruminants in the EU and the minimum requirements for the recognition of the 'negligible risk of classical scrapie status' are different because they are not based on the same assumptions, hence compliance with the former does not mean automatic compliance with the latter.

4.2. Historical surveillance

The results of the estimation of the overall sensitivity of the surveillance system (i.e. the level of confidence of disease detection mentioned in the ToR) using scenario-tree modelling with parameters as described in Section 2.2.2 and with data as in Table 2 reveal that:

- During the period 2008-2014 and using the test sensitivity derived from the EU test evaluation data and alternative scenarios, Sweden has tested annually a sufficient number of ovine and caprine animals over 18 months of age, sourced from the NSHC and SHC, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%.

4.3. Future surveillance

The results of the estimation of the overall sensitivity of the surveillance system (i.e. the level of confidence of disease detection mentioned in the ToR) using scenario-tree modelling with parameters as described in Section 2.2.2 and with data as in Table 2 reveal that:

- Based on the expected number of samples to be tested in 2015 and future years and on the test sensitivity derived from the EU test evaluation data, Sweden would test annually a sufficient number of ovine and caprine animals over 18 months of age, sourced from the NSHC and SHC, to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1%.
- Based on the expected number of samples to be tested in 2015 and future years and on the results of the alternative test sensitivity scenarios, Sweden would test a sufficient number of animals to provide a 95% level of confidence of detecting CS if it is present in that population at a prevalence rate exceeding 0.1% if the actual test sensitivity under field conditions was higher than 80%.

5. Recommendations

- In 2013 the EC produced guidelines for drafting a dossier for the recognition of an MS or zones of an MS with a negligible risk of CS. It is recommended that this guideline document includes agreed specific methodologies, to be used by other MS when preparing their applications.
- The sensitivity of the screening tests in field conditions is a critical parameter when estimating the overall sensitivity of the surveillance system. There is a lack of data of the actual performance of the approved tests in field conditions. It would be advisable to generate such data.
- The parameters used in this assessment are dynamic. Prior to the assessment of any subsequent application, parameters relating to risk factors and test sensitivity should be reviewed and, if necessary, updated.

Documentation provided to EFSA

1. Report on risk assessment and estimation of probability of freedom from classical scrapie in sheep and goats in Sweden. SVA Dnr 2014/674 SJV 6.2.18 -8583/14. 15 August 2015

2. Questions and comments on Sweden's application for negligible risk status for classical scrapie. 3 November 2014.

3. The Swedish application for classical scrapie negligible risk, an update of the answers to point c, to include the surveillance figures for 2013 and 2014. 2 March 2015.

4. Figure. Scenario tree. Email attachment. 21 October 2014.

5. Questions and comments on Sweden's application for negligible risk status for classical scrapie. 21 July 2015.

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Abbreviations

AS	atypical scrapie
BIOHAZ	Biological Hazards
BSE	bovine spongiform encephalopathy
CI	confidence interval
CNS	central nervous system
CS	classical scrapie
DP	design prevalence
EC	European Commission
EPI	effective probability of infection
GSe	group sensitivity
IRMM	Institute for Reference Materials and Measurements
LRS	lymphoreticular system
MS	Member State
NSHC	not slaughtered for human consumption
OIE	World Organisation for Animal Health
PR	prevalence ratio
PrP	prion protein
PrP^{C}	cellular prion protein
PrP^{Sc}	abnormal isoform of the cellular prion protein
RiBESS	risk-based estimate of system sensitivity tool
RSe	sensitivity of round of testing
SHC	slaughtered for human consumption
SSe	overall sensitivity of the surveillance system
TSe	test sensitivity
ToR	Terms of Reference
TSE	transmissible spongiform encephalopathy
WG	Working Group
WR	weighted risk

Appendix A – Description of the EU scrapie surveillance data

The first dataset included testing data by species from both passive and active surveillance and from the eradication cull of animals from outbreaks. The individual record was based on aggregated data by sampling year, target group (i.e. the surveillance stream) and country, providing the total number of tested animals, and of positive and negative/inconclusive results.

Only the data relating to the two main streams 'Not slaughtered for human consumption' i.e. fallen stock (NSHC) and 'slaughtered for human consumption' i.e. healthy slaughtered animals (SHC) were kept in the dataset, aggregated by year and comprising 5 669 785 sheep and 1 939 423 goats. Further restrictions were applied in three subsets of the full data:

- for the same MS, years in which there have been cases only in one single species in either SHC or NSHC;
- for the same MS, years in which the number of tested animals was < 385 in either SHC or NSHC;
- SHC and NSHC data in the category 'TSE infected flocks under official control at sampling' (Note: before 2006, very few data points fell in this category since compulsory eradication measures were mainly enforced in later years and differentiated in the reports)

The results of removing data falling into the three categories as above produced a final dataset for analysis containing a total of 3 927 143 tested sheep and 412 391 tested goats with results.

A second dataset of individual case data included information (e.g. country, year of sampling, species, surveillance stream) on each individual scrapie case confirmed in the EU. This dataset made it possible to discriminate between CS and AS cases allowing the elimination of the latter. Before any data analysis, as for the testing datasets, all cases detected in categories other than those of active surveillance (i.e. NSHC and SHC) were dropped.

The case type category was largely missing in the period before 2006 when an EU system of automatic upload was set up. Therefore, it was decided to consider also as CS cases those cases that before 2006 were categorised as unknown or for which the case type variable was missing.

Data collation, manipulation, cleaning and analyses were conducted using Stata (v13.1; Stata Corp, College Station, TX, USA).

Appendix B – Results of the evaluation of *post-mortem* rapid tests for detection of TSE in small ruminants

Table 5 shows a summary of the results of the different evaluations of *post-mortem* rapid tests for the detection of TSE in small ruminants.

Table 5: Results of the EU evaluation of *post-mortem* screening diagnostic tests (rapid tests) for the detection of TSE in small ruminants (sources: EFSA 2005a,b; EFSA BIOHAZ Panel, 2012; IRMM 2005a,b,c, 2010)

Rapid test	Diagnostic sensitivity (%)	Number of positive brainstem samples tested	95% CI (%)		Rapid test still approved (yes/no)	IRMM report on the evaluation	EFSA report/opinion on the evaluation
Prionics Check PrioSTRIP SR (Visual protocol)	100.00	199	98.11	100.00	Yes	IRMM (2010)	EFSA BIOHAZ Panel (2012)
	100.00	50 (autolysed)	92.87	100.00			
Bio-Rad TeSeE	99.60	246	98.10	99.99	Yes	IRMM (2005a)	EFSA (2005a)
Bio-Rad TeSeE Sheep/Goat	100.00	246	98.80	100.00	Yes	IRMM (2005a)	EFSA (2005a)
Enfer	100.00	246	98.80	100.00	No (approved until end of 2010)	IRMM (2005a)	EFSA (2005a)
Institut Pourquier	100.00	245	98.80	100.00	No (approved until February 2009)	IRMM (2005a)	EFSA (2005a)
Prionics Check LIA SR	100.00	246	98.80	100.00	No (approved until end of 2010)	IRMM (2005a)	EFSA (2005a)
Prionics Check Western SR	100.00	246	98.80	100.00	No (approved until end of 2010)	IRMM (2005a)	EFSA (2005a)
IDEXX HerCheck BSE	100.00	245	98.80	100.00	Yes	IRMM (2005b)	EFSA (2005b)
Beckman Coulter's InProCDI	100.00	246	98.80	100.00	No (approved until February 2009)	IRMM (2005c)	EFSA (2005b)