

SCIENTIFIC OPINION

Scientific Opinion on the revision of the quantitative risk assessment (QRA) of the BSE risk posed by processed animal proteins (PAPs)¹

EFSA Panel on Biological Hazards (BIOHAZ)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The cattle Bovine Spongiform Encephalopathy (BSE) risk posed by bovine derived Processed Animal Proteins (PAPs) in feed was estimated, the diagnostic methods and their sensitivity to detect animal proteins in feed and compared different risk assessment methods for animal proteins in feed was reviewed. It was concluded that the current global limit of detection for PAPs in feed is still considered to be 0.1%. Data related to BSE monitoring and PAP production in the European Union (EU) were considered. A model (EFSA QRA PAP model) was developed to study the magnitude of the total BSE infectivity in PAPs and in ruminant feed under a certain scenario assuming some specific cross-contaminations. On the basis of the 2009 BSE surveillance data in the EU, assuming a 0.1% contamination (the limit of detection for PAP in feed) with non-ruminant PAPs and according to the EFSA QRA PAP model, the total BSE infectivity load that could enter in cattle feed per year in the EU would be equivalent to 0.2 Cattle oral Infectious Dose 50%⁴ (Co ID₅₀) ($9 \times 10^{-5} - 1.3$ CI95%) (that would mean that less than one additional BSE infected cattle could be expected in the EU cattle population per year with an upper 95% confidence). The specific scenario described by the model and the related assumptions and uncertainties are discussed in this scientific opinion.

© European Food Safety Authority, 2011

KEY WORDS

Bovine Spongiform Encephalopathy (BSE), quantitative risk assessment, Processed Animal Proteins (PAP), Cat 3 Animal By-Products

¹ On request from the European Commission, Question No EFSA-Q-2010-00001, adopted on 09 December 2010.

² Panel members: Olivier Andreoletti, Herbert Budka, Sava Buncic, John D Collins, John Griffin, Tine Hald, Arie Havelaar, James Hope, Günter Klein, James McLauchlin, Christine Müller-Graf, Christophe Nguyen-The, Birgit Noerrung, Luisa Peixe, Miguel Prieto Maradona, Antonia Ricci, John Sofos, John Threlfall, Ivar Vågsholm and Emmanuel Vanopdenbosch. Correspondence: biohaz@efsa.europa.eu

³ Acknowledgement: The Panel wishes to thank the members of the Working Group on the review of the QRA of the residual BSE risk of MBM: Amie Adkin, Olivier Andreoletti, Philip Comer, Christian Ducrot, Michael Gravenor, Matthias Greiner, James Hope, Christine Müller-Graf and Emmanuel Vanopdenbosch for the preparatory work on this scientific opinion.

⁴ The oral dose which infects 50% of cattle in an experimental test.

Suggested citation: EFSA Panel on Biological Hazards (BIOHAZ); Scientific Opinion on the revision of the quantitative risk assessment (QRA) of the BSE risk posed by processed animal proteins (PAPs). EFSA Journal 2011;9(1):1947. [80 pp.] doi:10.2903/j.efsa.2011.1947. Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission (EC), the Panel on Biological Hazards (BIOHAZ) was asked to deliver a scientific opinion on the revision of the Quantitative Risk Assessment (QRA) of the Bovine Spongiform Encephalopathy (BSE) risk posed by Processed Animal Proteins (PAPs)⁵.

The feed ban is the key animal health protection measure against Transmissible Spongiform Encephalopathies (TSEs) and consists of a ban on the use of animal proteins in feed for farmed animals. Scientific data link the spread of BSE to the consumption of feed contaminated by the infected ruminant proteins. Based on these findings a ban on the feeding of mammalian PAPs to cattle, sheep and goats was introduced in July 1994. The ban was expanded in January 2001 with the feeding of all PAPs to all farmed animals being prohibited, with certain limited exceptions. Any presence of prohibited constituents of animal origin in feed is considered as a breach of the feed ban i.e. the zero-tolerance.

The overall decrease in the numbers of BSE cases across the European Union (EU) (about 2,167 BSE cases in 2001 in the EU 15, compared to 125 cases in the 2008 and only 45 up to the end of November 2009 in the EU 27) clearly demonstrates a continuous positive trend in the eradication of the disease. Therefore the EC asked the European Food Safety Authority (EFSA): i) to review and update the scientific input data of the current EFSA QRA model (“EFSA QRA Report 2004 on quantitative assessment of the residual BSE risk in bovine-derived products.”)⁶; ii) if needed, to review the methodology and update the current QRA model; and iii) to review the cattle BSE risk posed by bovine derived PAPs with respect to the residual BSE risk, based on the outcome of the QRA.

The BIOHAZ Panel addressed the mandate by: i) reviewing the diagnostic methods and their sensitivity to detect animal proteins in feed; ii) comparing different risk assessment models for animal proteins in feed; and iii) updating the scientific input data and the previous EFSA QRA model under a specific scenario. Moreover, some considerations about Atypical BSE were taken into account.

It was concluded that the current global limit of detection for PAPs in feed is still considered to be 0.1%. The structure of the EFSA QRA model was considered to be still suitable for the purpose of the mandate received and an updated version of that model (called EFSA QRA PAP model) was developed to answer the specific terms of reference of the mandate.

The EFSA QRA PAP model relies on the continuation of the current Specified Risk Material (SRM) policy and TSE monitoring system. It also assumes that only Category 3 Animal By-Product material is allowed to enter in PAP produced from ruminant material. The model is based on a specific scenario and on specific assumptions like the homogeneous mixing of the material for feed production. While conservative values were used, uncertainties of certain parameters were identified; changes in scientific knowledge would require an adjustment of the model. The model calculations are based on the presently available data, including unofficial ones, about PAP production communicated directly by industry; changes in PAP and feed production would require adjustment of the model input data.

On the basis on the 2009 BSE surveillance data, assuming a 0.1% contamination (which is the limit of detection for PAPs in feed) with non-ruminant PAP and according to the EFSA QRA PAP model, the Panel concluded that the total BSE infectivity load that could enter in cattle feed per year in the EU would be

⁵ According to Commission Regulation (EC) No 829/2007 of 28 June 2007 they are defined as: “animal protein derived entirely from Category 3 material, which have been treated in accordance with Chapter II of Annex VII so as to render them suitable for direct use as feed material or for any other use in feedingstuffs, including petfood, or for use in organic fertilisers or soil improvers; however, it does not include blood products, milk, milk-based products, colostrum, gelatine, hydrolysed proteins and dicalcium phosphate, eggs and egg-products, tricalcium phosphate and collagen”.

⁶ EFSA (European Food Safety Authority), 2005. EFSA QRA Report 2004 on quantitative assessment of the residual BSE risk in bovine-derived products. The EFSA Journal, 307, 1 - 135.

equivalent to 0.2 Cattle oral Infectious Dose 50%⁷ (Co ID₅₀) (9×10^{-5} – 1.3 CI95%) (that would mean that less than one additional BSE infected cattle could be expected in the EU cattle population per year with an upper 95% confidence).

It was highlighted that considering the many uncertainties related to Atypical BSE (prevalence, tissue distribution of the infectious agent, efficacy of rendering process for agent inactivation) the risk of Atypical BSE transmission through PAPs cannot be assessed but should not be disregarded.

It was recommended to continue the development of analytical methods to improve the limit of detection of animal proteins in feed and to take into account the risk of (re-)emergence of TSE in cattle in case the use of some mammalian PAPs for feeding animals should be reintroduced. Moreover, in case of modification of the mitigation measures against BSE the assessment should be updated.

Furthermore, the BIOHAZ Panel recommended to: i) collect specific data related to the PAP production and distribution system; ii) expand specific knowledge related to Atypical BSE (in particular as regards to prevalence, pathogenesis in natural host, capacity to propagate in other animal species and resistance to inactivation processes applied in rendering plants); and iii) to revise the assessment when appropriate information on Atypical BSE becomes available.

⁷ The oral dose which infects 50% of cattle in an experimental test.

TABLE OF CONTENTS

Abstract	1
Summary.....	2
Table of contents	4
Background as provided by the European Commission.....	7
Terms of reference as provided by the European Commission.....	7
Assessment	8
1. Introduction	8
2. Update on the performance of the methods for detection of Animal Proteins (APs) and Processed Animal Proteins (PAPs) in feedingstuffs	11
2.1. Classical microscopy for AP and PAP detection.....	11
2.2. Near Infrared Microscopy (NIRM) for AP and PAP detection	11
2.3. Immunoassays for PAP detection	11
2.4. Polymerase Chain Reaction (PCR) for PAP detection	11
2.5. Combination of methods.....	12
2.6. Conclusions on the performance of the methods for detection of APs and PAPs in feedingstuffs.....	14
3. Review of the EFSA QRA model.....	15
3.1. Comparison of risk assessments investigating the risk of processing meat and bone meal for non-ruminant feed.	15
3.1.1. Approaches and parameterisation.....	15
3.1.2. Contamination routes investigated	16
3.1.3. Results from the studies.....	16
3.1.4. Conclusions from comparison	16
4. Probabilistic Model for the Quantitative Assessment of Residual BSE Risk of Processed Animal Protein in Cattle Feed.....	18
4.1. Introduction.....	18
4.2. Model Basis and Structure.....	18
4.2.1. Model structure.....	18
4.2.2. Model basis.....	18
4.2.3. BSE infectivity in Ruminant PAP	19
4.3. Input data	19
4.3.1. Prevalence.....	19
4.3.2. Yield of by-products per animal.....	21
4.3.3. Proportion of ruminant Cat. 3 material of bovine origin.....	21
4.3.4. Batch size.....	21
4.3.5. PAP yield.....	21
4.3.6. Probability of SRM incomplete removal and quantity of SRM remaining tissue per animal	21
4.3.7. Infectivity of Bovine Tissues.....	23
4.3.8. Exposure of Cattle Feed to Ruminant PAP	25
4.3.9. PAP and Ruminant Feed Production	26
4.3.10. Reduction in infectivity by processing.....	26
4.3.11. Consumption of Feed Concentrate	27
4.4. Results of the EFSA QRA PAP model.....	28
4.4.1. Total infectivity	28
4.4.2. Individual Cattle Exposure	29
4.4.3. Discussion of results.....	29
4.4.4. Sensitivity analysis	30
4.5. Model validation and brief consideration on R_0	31
4.5.1. Conclusions	33

5.	Considerations on Atypical BSE	34
5.1.	Conclusions on Atypical BSE.....	35
	Conclusions and recommendations	36
	Documentation provided to EFSA	37
	References	38
A.	Appendix I: Comparison of the key parameters and components in four MBM risk assessments	42
B.	Appendix II: Detailed description of the EFSA QRA PAP model.....	45
1.	General description of the model	45
1.1.	Background	45
1.2.	Objectives	45
1.3.	Scope.....	45
1.4.	Model concept.....	45
2.	Model uncertainties and knowledge base.....	46
2.1.	Qualitative scoring system.....	46
2.2.	Assessment of general model uncertainties	47
2.3.	Assessment of scenario uncertainty	48
2.4.	Assessment of modelling approach uncertainty	50
3.	Model structure and contents.....	53
3.1.	Input Data Sheet.....	57
3.1.1.	Item D1: Number of cattle tested BSE positive	57
3.1.2.	Item D2: Number of cattle tested	57
3.1.3.	Item D3: Number of cattle slaughtered	57
3.1.4.	Item D4: Ratio undetected to detected BSE cases.....	58
3.1.5.	Item D5: BSE infectivity in bovine brain.....	58
3.1.6.	Item D6: Yield of by-products.....	59
3.1.7.	Item D17: Probability of incomplete removal of SRM	59
3.1.8.	Item D18: Infected tissue per contaminated animal	60
3.1.9.	Item D19: Batch size	60
3.1.10.	Item D20: Batch size equivalent to model a continuous process	61
3.1.11.	Item D21: Yield of PAP from processed by-products	61
3.1.12.	Item D22: Proportion of ruminant PAP produced from bovine material	62
3.1.13.	Items D23 and D24: BSE infectivity reduction by processing.....	62
3.1.14.	Item D25: Proportion of contamination of non-ruminant PAP with ruminant PAP	63
3.1.15.	Item D26: Contamination of ruminant feed with non-ruminant PAP	63
3.1.16.	Items D27 and D28: Daily consumption of cattle feed concentrate.....	64
3.1.17.	Items D29, D30, D31 and D32: Total PAP produced in EU	64
3.1.18.	Item D33: Total cat 3 ruminant material processed	65
3.1.19.	Item D34: Total ruminant feed produced in EU.....	65
3.2.	PAP to Cattle Sheet.....	66
3.2.1.	Item P1: Prevalence Data Used	66
3.2.2.	Items P2 and P3: BSE prevalence in slaughter cattle.....	66
3.2.3.	Item P4: Selected Batch size	66
3.2.4.	Item P5: Yield of By-Products per animal	67
3.2.5.	Item P6: Number of cattle contributing to one batch	67
3.2.6.	Item P7: Number of BSE infected cattle per batch	67
3.2.7.	Item P8: Probability of SRM incomplete removal.....	68
3.2.8.	Item P9: Quantity of remaining SRM tissues per animal	68
3.2.9.	Item P10: Sampled BSE infectivity in bovine brain.....	68
3.2.10.	Item P11: Infectivity per infected animal	69
3.2.11.	Item P12: Total BSE infectivity per batch of PAP.....	69
3.2.12.	Item P13: BSE infectivity reduction during processing	69
3.2.13.	Item P14: BSE infectivity in ruminant PAP	70

3.2.14.	Item P15a: Proportion of contamination of non-ruminant PAP with ruminant PAP	70
3.2.15.	Item P15: BSE infectivity of non-ruminant PAP.....	70
3.2.16.	Item P20: Sampled daily consumption of cattle feed concentrate.....	71
3.2.17.	Items P21, P22 and P23: Non-ruminant PAP in cattle feed	71
3.2.18.	Items P28, P31 and P34: Exposure to infectivity	71
3.3.	Sheet 3: Total Exposure.....	72
3.3.1.	T1: Total cat 3 ruminant material processed.....	72
3.3.2.	Item T2: PAP produced from ruminant Category 3 ABP.....	72
3.3.3.	Item T3: Number of BSE positive cases.....	72
3.3.4.	Item T4: Number of undetected infected cattle	72
3.3.5.	Item T5: Quantity of remaining SRM tissues per animal.....	73
3.3.6.	Item T6: Probability of SRM incomplete removal.....	73
3.3.7.	Item T7: Sampled BSE infectivity in bovine brain	73
3.3.8.	Item T8: Total infectivity in Cat 3 ABP.....	73
3.3.9.	Item T9: Concentration in ruminant PAP.....	74
3.3.10.	Items T10, T11 and T12: Non-ruminant PAP produced in EU in 2009.....	74
3.3.11.	Item T3: Total non-ruminant PAP produced in EU in 2009	74
3.3.12.	Item T14: Proportion of contamination of non-ruminant PAP with ruminant PAP.....	74
3.3.13.	Item T15: Amount of ruminant PAP present in non-ruminant PAP.....	75
3.3.14.	Item T16: Proportion of total ruminant PAP	75
3.3.15.	Item T17: Total infectivity in non-ruminant PAP	75
3.3.16.	Item T18: Concentration in non-ruminant PAP.....	75
3.3.17.	Item T19: Total ruminant feed produced in EU	76
3.3.18.	Item T20: Contamination of ruminant feed with non-ruminant PAP.....	76
3.3.19.	Item T21: Total non-ruminant PAP present in cattle feed	76
3.3.20.	Item T22: Proportion of total non-ruminant PAP.....	76
3.3.21.	Item T23: Total infectivity in ruminant feed.....	77
3.3.22.	Item T24: Calculation of R_0 values	77
	Glossary.....	78

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The feed ban is the key animal health protection measure against TSE (Transmissible Spongiform Encephalopathy) and consists of a ban on the use of processed animal protein (PAP) in feed for farmed animals. Scientific data link the spread of BSE (Bovine Spongiform Encephalopathy) to the consumption of feed contaminated by the infected ruminant protein in the form of PAP. Based on these findings a ban on the feeding of mammalian processed animal protein to cattle, sheep and goats was introduced in July 1994. The ban was expanded in January 2001 with the feeding of all processed animal proteins to all farmed animals being prohibited, with certain limited exceptions. Any presence of prohibited constituents of animal origin in feed is considered as a breach of the feed ban i.e. the zero-tolerance.

In the view of significant and overall decrease in the numbers of BSE cases across the EU (about 2,167 BSE cases in 2001 in the EU 15, compared to 125 cases in the 2008 and only 45 up to the end of November 2009 in the EU 27) clearly demonstrate continuing positive trend in eradication of the disease.

In the summary to the opinion of the Scientific Panel on Biological Hazards (BIOHAZ) on the “Quantitative risk assessment of the animal BSE risk posed by meat and bone meal with respect to the residual BSE risk” (EFSA-Q-2003-099, July 2005) it was stated, that the QRA Report should be considered a dynamic document and, consequently, its content and data need to be reviewed periodically

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Food Safety Authority is requested therefore to:

- To review and update the scientific input data of the QRA
- If needed, to review the methodology and update the QRA
- To review the animal BSE risk posed by meat and bone meal with respect to the residual BSE risk, based on the outcome of the QRA

Clarification on the Terms of Reference

After discussion with the requestor it was agreed to modify the terms of reference as reported here below:

- To review and update the scientific input data of the current QRA model.
- If needed, to review the methodology and update the current QRA model.
- To review the cattle BSE risk posed by bovine derived processed animal proteins (PAPs) with respect to the residual BSE risk, based on the outcome of the QRA.

ASSESSMENT

1. Introduction

A feed ban was first introduced by the European Commission (EC) in 1994 on the use of processed mammalian animal proteins in feed for ruminants to reduce and stop the spread of the BSE epidemic⁸. A Scientific Steering Committee (SSC) report from 1998 states that “*The Scientific Steering Committee is of the opinion that in principle, cross-contamination with mammalian meat and bone meals of animal feedstuffs is not acceptable and that only a zero level of cross-contamination can exclude any risk resulting from it.*”(SSC, 1998). The feeding ban was extended in 2001 with a prohibition of feeding of all processed animal proteins to all farmed animals (with few exceptions)⁹. This ban is still in place, although the incidence of Classical BSE has decreased. To evaluate the residual BSE risk in bovine derived products an EFSA report was developed in 2004 analysing the situation with the help of a quantitative model (EFSA, 2005a). The SSC report did not use a model. This quantitative model was based on a probabilistic approach using Monte Carlo simulations and carried out in @RISK, an EXCEL based spreadsheet application. Built on the 2004 model in 2005 an EFSA opinion was written to re-evaluate the data on the BSE risk posed by Meat-and-Bone Meal (MBM) (EFSA, 2005b). The model used in the 2005 opinion - subsequently called EFSA QRA model - was a reduced version of the model in the 2004 QRA report, since this dealt with more questions than only the risk of MBM. In the 2005 opinion the input data were updated according to the latest scientific information. The results did not change the conclusions of the previous report from 2004.

The EFSA 2005 opinion concluded that cattle in an intensive system obtaining about 8 kg of compound feed containing 0.1% MBM with a 40% bovine origin from a GBR IV country with unreliable surveillance and where no Specified Risk Materials (SRMs)¹⁰ were removed prior to rendering, could be exposed to a median of 5×10^{-5} Cattle oral Infectious Doses 50% (Co ID₅₀)¹¹ units per animal per year, that is in a population of 1 million cattle a median of 25 cattle could become infected. For the same scenario if all SRMs were removed then the median risk would be 8.1×10^{-7} Co ID₅₀. For a GBR III country with reliable surveillance and SRMs removed – more comparable to the present situation - the median would be 0, the mean 1.2×10^{-7} (0.6 animals in a 1 million cattle) and the 97.5 Percentile 7.8×10^{-7} that is 0.39 cattle could be expected to be infected in 1 million cattle.

The EFSA QRA model was considered a dynamic document which had to be revised in light of new information. This new mandate will be looking at the model to discuss whether new information or newly developed modelling techniques warrant a different approach.

This new opinion deals first with the diagnostic methods and sensibility to detect animal proteins in animal feed. These are pivotal to control the feeding ban and any possible relaxation.

To assess whether there is a need to change the methodology of the present model, published models on the same subject of risk of MBM are analysed. The possibility of a validation is discussed. The input parameters for the model are compared with new available information, especially since in the older model only data pre-dating the feeding ban of 2001 were used. Particular attention is given to the present prevalence of BSE and the possible undetected BSE cases as well as the possibility of more up-to-date information on the infective tissues. Further sensitivity analysis – that is the impact of a specific parameter on the model results - is included. The quantitative results are discussed with view to the previous results. In this opinion not

⁸ 94/381/EC: Commission Decision of 27 June 1994 concerning certain protection measures with regard to bovine spongiform encephalopathy and the feeding of mammalian derived protein. OJ L 172, 7.7.1994, p. 23–24.

⁹ 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, 31.5.2001, p. 1–40.

¹⁰ For a definition of the SRMs please refer to the glossary

¹¹ The oral dose which infects 50% of cattle in an experimental test.

only Classical BSE – the pathogen at the origin of the BSE epidemic - but also Atypical BSE is considered. Since the decline of the prevalence of Classical BSE the atypical forms have received more attention.

The previous model looked at MBM. According to Directive 92/87/EEC¹² MBM is a product with certain characteristics obtained from Animal By-Products (ABPs), rendered animal proteins possibly coming also from high risk material. This Directive does not classify the raw material according to its risk. There are other sources of animal proteins than MBM: e.g. Meat Meal (MM).

After discussion for clarification of the mandate it was decided to only consider the Processed Animal Proteins (PAPs), which belong to Category (Cat.) 3 ABPs that are derived from low risk material according to Reg. (EC) 1774/2002¹³ as amended, in the model, which is subsequently referred to as EFSA QRA PAP. PAPs can comprise MBM and other types of animal proteins such as MM. But of course these shall derive from low risk material (Cat 3 ABPs).

Cat. 3 material is roughly defined as the following (for detailed information see the above cited regulation): parts of slaughtered animal which are fit for but not intended for human consumption, part of animals which are rejected as unfit for human consumption but derive from carcasses that are fit for human consumption, hides, skins, hooves, horns, blood and animal by-products derived from products for human consumption.

According to Regulation (EC) 829/2007¹⁴ PAP is defined as “*animal protein derived entirely from Category 3 material, which have been treated in accordance with Chapter II of Annex VII so as to render them suitable for direct use as feed material or for any other use in feedingstuffs, including petfood, or for use in organic fertilisers or soil improvers; however, it does not include blood products, milk, milk-based products, colostrum, gelatine, hydrolysed proteins and dicalcium phosphate, eggs and egg-products, tricalcium phosphate and collagen*”.

Cat. 1 and 2 ABPs are destroyed or used in landfill or fertilizers or some other means as specified in the legislation and could thus not legally enter into the feed chain. Therefore, Cat. 1 and 2 ABPs are not considered in this opinion.

The model in this opinion looks only at a specific scenario to study the risk of infectious BSE material in ruminant feed (see figure 1). Cat.3 material is considered to contain no infectious material. However, there may be a certain possibility that not all bovine SRM has been completely removed and some material may enter into bovine Cat.3 material. In this model, it is assumed between 0.1% - 5% bovine SRM material can enter bovine Cat.3 material. The second step of the model assumes then that this bovine Cat.3 material is used to produce ruminant PAP. The amount of bovine Cat.3 material used to produce ruminant PAP is set at the level of 90%. The third step in the scenario is that it is assumed that non-ruminant PAP may be contaminated with ruminant PAP and it is presumed that this contamination could range from zero to 5%. The last step would be that ruminant feed is contaminated by the above mentioned non-ruminant PAP contaminated by ruminant PAP with possibly infectious material due to non-complete removal of bovine SRM – explained in the previous steps - at three particular concentrations 0.02%, 0.1.% and 2%. The concentration of 0.1 % was chosen, because of the limits of diagnostic detections and the other ones were selected to be comparable with the previous opinion. The model does not consider various concentrations, to obtain an idea of a threshold of contamination. This model does not consider any other options of infectious PAP entering the system – such as fertilizer – nor can it deal with a situation where ruminant PAP is

¹² Commission Directive 92/87/EEC of 26 October 1992 establishing a non-exclusive list of the main ingredients normally used and marketed for the preparation of compound feedingstuffs intended for animals other than pets. OJ L 319, 4.11.1992, p. 19–32.

¹³ Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption. OJ L 273, 10.10.2002, p. 1–95.

¹⁴ Commission Regulation (EC) No 829/2007 of 28 June 2007 amending Annexes I, II, VII, VIII, X and XI to Regulation (EC) No 1774/2002 of the European Parliament and of the Council as regards the placing on the market of certain animal by-products. OJ L 191, 21.7.2007, p. 1–99.

deliberately entering the system of ruminant feed production. A further model assumption is that other measures such as the current BSE testing and surveillance are still in place.

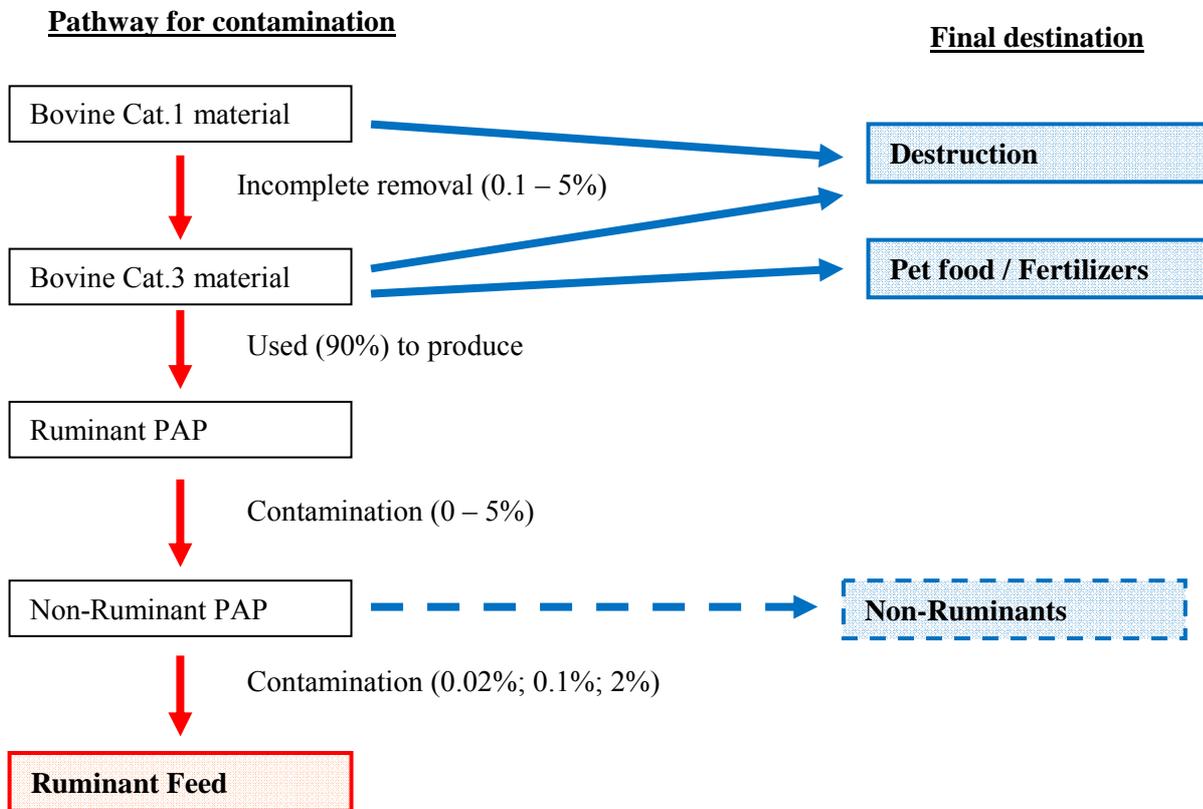


Figure 1: Main pathways of the EFSA QRA PAP Model. The figures given are the assumptions of the model. Current and proposed pathways, and potential contamination pathways are as follows:

-  Current legal pathway (not exhaustive)
-  Possible future pathway
-  Contamination pathway

2. Update on the performance of the methods for detection of Animal Proteins (APs) and Processed Animal Proteins (PAPs) in feedingstuffs

Since the last EFSA opinion (2007a), some new aspects about the performances of the different methods can be highlighted and are reported in the following sections.

Moreover, an updated summary of performance characteristics of the different methods is given in Table 1. More details on the methods may also be found in general reviews on the topic (Fumiere et al., 2009; Veys and Baeten, 2010).

2.1. Classical microscopy for AP and PAP detection

The official method has been harmonized among the National reference laboratories (NRL) of the Member States on several points that were not detailed sufficiently in the method that appeared in Annex VI of Regulation (EC) 152/2009¹⁵.

Detection of PAPs and APs in feed by classical microscopy generally has a limit of detection that is much lower than 0.1%. For instance the PAP sample used in the CRL-AP PT2009 study (Veys and Baeten, 2010) could be detected at a level as low as 0.0025% in feed. However, for difficult samples such as terrestrial PAPs within fish meals, this method is not as sensitive. Therefore, overall the limit of detection of this method should still be considered as a level of 0.1%.

2.2. Near Infrared Microscopy (NIRM) for AP and PAP detection

NIRM methods use the infrared spectra of particles to determine their origin. The NIR microscopy method developed at Walloon Agricultural Research Centre (CRA-W) has been successfully transferred to another lab (von Holst et al., 2008) and can analyze small particles (~50 µm of diameter).

The key parameters for a quantitative method based on NIRM have been identified (Abbas et al., 2010). However, the quantification results showed a systematic underestimation and the reproducibility of the NIR microscopic method at its present development stage is not better than the one observed with classical microscopy. NIRM is less subjective than classical microscopy and for this reason is worth pursuing.

2.3. Immunoassays for PAP detection

In the context of a global detection strategy for processed animal proteins immunoassays are essentially used as screening tests. This method may be particularly useful when testing for the presence of well-defined species or groups of species in other PAPs (*e.g.* a rapid test for detection of ruminant material in other PAPs). However, the existing assays do not yet meet the minimal performance requirements (limit of detection < 2% for PAP of one species or one group of species in PAP of another species or group of species) to be able to proceed to routine application of the technique. Performance characteristics in terms of sensitivity have not evolved since the last EFSA opinion on this topic.

2.4. Polymerase Chain Reaction (PCR) for PAP detection

Even if it was known that PCR could be used at least for qualitative tests (Prado et al., 2007), there was still some concern for its use in a network of laboratories. Now the transferability of the method has been achieved (Fumiere et al., 2010). The sensitivity of the method has not been improved, but it was not a

¹⁵ Commission Regulation (EC) No 152/2009 of 27 January 2009 laying down the methods of sampling and analysis for the official control of feed OJ L 54, 26.2.2009, p. 1–130.

limiting factor, and problems for interpretation of PCR results - due to authorized animal material in feed that can be a source of DNA targets - remain. However, proof of concept was given that a way to circumvent this last drawback would be to combine NIRM and PCR. Therefore this combination should further be tested in real life conditions to assess its potential for routine application.

2.5. Combination of methods

As one of the major problems for PCR is its inability to discriminate DNA from authorized and unauthorized material one approach would be to combine it with a method without this problem such NIRM. NIRM can distinguish animal particles from particles of other origin but PCR could then be used on the particles identified as animal ones to identify its species of origin. A protocol to make DNA extractions giving material fit for PCR has been developed for such single particles (Fumiere et al., 2010). Nevertheless it was also shown that when mixing several ingredients for instance milk powder with pig PAPs, the pig particles isolated by NIRM (as terrestrial particles) could contain bovine DNA due to contamination at the outer surface of the particle with milk powder that still might contain bovine DNA. Therefore purification protocols of the particles had to be tested and of the several protocols tested, one was much better than all the others (Fumiere et al., 2010). This combination remains to be assessed under field conditions.

Table 1: Summary of the performance characteristics of the different detection methods

	Classical microscopy	NIRM	Immunoassay	PCR
Analytical features				
Official method	yes	no	no	no
Samples/day	5	3-5	100-200	10-20
Analytical time/sample	½ day	½ day	1 h – 1 day ¹	1½-2 days
Sampling	5-10 g	0.2-10 g	~ 10 g	≥ 0.1 g
Transferability	medium-high ²	High	high	medium to high ³
Matrix-dependent	no ⁴	no ⁴	yes	yes
Rendering-process dependent	no	no	yes ⁵	yes ⁵
Animal-tissue dependent	yes	no	yes	limited ⁶
Species or species-group discrimination	limited	limited	yes	yes
LOD for detection of PAP in feed	< 0.1%	< 0.1% ⁷	~ 0.5 %	< 0.1 % ⁸
LOD for detection of PAP in PAP	~ 0.1% ⁹	< 0.5 % ¹⁰	~ 2 % or more	< 0.5%
Quantitative possibilities	possible but high Relative Reproducibility Standard Deviation	under investigation	no data	not considered
Interfering features				
Other authorized products	no	no	yes/no ¹¹	yes
Fat	no	no	sometimes	sometimes
Particle size influence	no	no	no	no
Miscellaneous				
Fully validated (inter-laboratory study)	yes	yes (in progress)	no ¹²	yes
Existing facilities	yes	yes (limited)	yes	yes
Experience of operator required	high	moderate	low to moderate	moderate to high
Equipment costs	moderate	high	low to moderate ¹	high

1. depends if it is a lateral flow assay (which might be a dipstick in some cases) or an ELISA
2. largely linked to experience of the operator
3. transferability is improved with the design of a protocol for defining a cut-off value independent of the PCR platform used
4. not applicable to liquids however
5. most commercial PAP produced in Europe remains detectable however by PCR or by immunoassays – very high temperatures are costly in use of energy
6. the limit is linked to the fact that DNA should still be present which is mostly the case
7. LOD here is also linked to the number of particles analysed – to reach this level at least 3000 particles have to be analysed
8. value generally valid on PAPs produced in the European Union
9. applicable only for terrestrial AP or PAP to be detected in fish meal
10. no lower quantity than 0.5% of PAP in PAP was investigated up to now
11. depends on the target used, e.g. if troponin is the antigen there is no interaction with milk or milk powder
12. not validated in an inter-laboratory comparison

2.6. Conclusions on the performance of the methods for detection of APs and PAPs in feedingstuffs

Since the 2007 EFSA opinion:

- Microscopy theoretical Limit Of Detection (LOD) for APs and PAPs was shown to be far below 0.1%. However, considering difficult situations like terrestrial animal particles that have to be detected in presence of fish meal, the global LOD of the method is maintained at 0.1%.
- Immunoassays even though of interest in a global detection strategy of PAPs do not meet the minimal performance requirements (LOD < 2% for PAP of one species or one group of species in PAP of another species or group of species).
- PCR methodology for PAPs is still suffering from specificity problems. False positive results being obtained due to authorized animal material that can be a source of DNA targets remain.
- The current global limit of detection for PAPs in feed is still considered to be 0.1%.

3. Review of the EFSA QRA model

3.1. Comparison of risk assessments investigating the risk of processing meat and bone meal for non-ruminant feed.

A comparison of the original EFSA risk assessment has been completed with other, more recent, risk assessments from published literature which quantitatively assess the amount of BSE infectivity in certain risk categories of meat and bone meal (MBM). For this comparison, only published risk assessments have been compared:

1. EFSA QRA model (EFSA, 2005a) Europe
2. Yamamoto et al., (2006) Japan
3. De Vos and Heres, (2009) Netherlands
4. Cummins and Adkin, (2007) UK and Ireland

The review focuses on the use of available data, approaches taken to estimate the risk, and conclusions. Some of these risk assessments subsequently address the risk posed from including MBM in non-ruminant feed due to different routes of contamination to ruminant feed or other routes of exposure to MBM. In summary, each of the risk assessments is structured in a relatively similar manner and assesses the risk quantitatively through the following stages:

- Number of BSE infected cattle entering MBM
- Clinical state
- Infectivity titre of tissues diverted to MBM
- Infectivity remaining post controls
- Infectivity remaining post rendering
- Contamination routes
- Amount consumed and where available, dose response

3.1.1. Approaches and parameterisation

Key assumptions and parameter comparisons between the four risk assessments are provided in Appendix I. From the table it can be seen that there are different assumptions made in each assessment and parameterisation of key components. Such differences may reflect the scientific knowledge available at the time of completion, the degree to which pessimistic assumptions are used, or the desired level of detail implemented in the risk assessment. Differences identified may not necessarily significantly impact the final model result, however, those thought to be of interest for further discussion are briefly summarised here.

The specification of the MBM, both in terms of sourced input material risk and rendering method applied, is important as it may significantly influence model assumptions. These may include the number of infected animals processed annually, which SRM and testing controls are applied, and which processing methods can legally apply. Additional to the specification of the MBM that is primarily focused on in each risk assessment is whether contamination by another category of MBM is considered, for example, Category 3 (low risk) MBM contamination with Category 1 (high risk).

There are significant differences in approaches to modelling the infectivity titre within infected carcasses. The de Vos & Heres model is the most detailed and mechanistic using the age at exposure, incubation period, and likely slaughter date to assess the clinical status of infected animals. Such an approach uses up to date scientific evidence to support the risk assessment, and allows a more realistic estimation of the infectivity titre of those animals by-passing controls in the Netherlands. However, this component does add considerably to the complexity of the risk assessment which increases the demands on report transparency and increases the country specific data required to parameterise.

3.1.2. Contamination routes investigated

The original EFSA QRA model evaluated three alternative thresholds of contamination of ruminant cattle feed with MBM. The limit of detection of the tests available to identify ruminant protein in feed is approximately 0.1%. This is used as a baseline, however the QRA working group had also requested that values of 0.02% and 2% contamination be evaluated. The remaining models have investigated the specific risk pathways associated. The Yamamoto model investigated three routes of exposure (i) feeding cattle concentrates with MBM as an ingredient; (ii) cross contamination of feed at feed mill; and (iii) other exposure e.g. fertiliser. The de Vos and Heres model investigated (i) cross contamination of feed at feed mill; and (ii) cross contamination on the primary farm; and (iii) exposure from pasture fertiliser. Finally, the Cummins and Adkin models investigated cattle exposure from fertiliser in the UK and Ireland. The approach of modelling individual pathways has the advantage of subsequently analysing the critical control points and for multiple pathways, investigating the relative risk of different routes of exposure.

3.1.3. Results from the studies

The results of the previous EFSA QRA model are not reiterated here, since they are already mentioned in the introduction of this opinion. The Yamamoto model estimated that the total infectivity fed to dairy cattle from one infected rendered animal via MBM was on average 0.49 Co ID₅₀, from which the authors concluded that the previous routes of exposure via Japanese MBM were unlikely to result in increased propagation of BSE in Japan. The de Vos and Heres model estimated a mean total of 1.8×10^{-4} ID₅₀ could be ingested by calves via the routes modelled. Based on these figures, the authors conclude that the overall BSE risk of using Category 3 MBM from Dutch cattle in non-ruminant feed is very low. However, mistakes in the processing of MBM may increase the risk substantially. When considering the fertiliser exposure route, Cummins and Adkin estimated that the mean level of infectivity in Category 3 MBM was 1.2×10^{-5} and 2.4×10^{-5} ID₅₀/tonne for the UK and Ireland respectively. The authors concluded that given the low risks to bovines, MBM could be used safely as a fertiliser.

3.1.4. Conclusions from comparison

When comparing the approaches developed in the reviewed risk assessments, each approach is bespoke to the risk question that is being addressed. The risk questions include details of the categories of MBM concerned, the country/territories addressed, and the level of detail required for the risk pathways. For example, the de Vos and Heres model was tasked with assessing the BSE risk for the Netherlands if Category 3 MBM was used in ruminant feed, whilst the Cummins and Adkin models were tasked with assessing the BSE risks for the UK and Ireland if Category 3 MBM was used as a fertiliser. The original EFSA risk assessment was tasked with assessing the BSE risk posed by MBM. With no specific exposure routes identified, the approach taken was to assume a threshold level of contamination of the MBM.

The approach of considering each risk pathway is likely to provide a more accurate representation of the risk via specific routes, however, more data and assumptions are required and therefore uncertainty bounds associated with the results may be wide. Whilst this approach has been successful

applied on a country specific basis where data are available, broadening such an approach for an EU wide risk assessment, taking into account the additional variability between countries would constitute a large undertaking. Therefore, to give an overview over the situation and changes brought about by the feeding ban, an updated version of the previous EFSA QRA model - a more general model -, is used in this opinion with an update to take into account the most recent information. For more specific questions and questions concerning particular countries or region, a more specific or different model may be more appropriate.

4. Probabilistic Model for the Quantitative Assessment of Residual BSE Risk of Processed Animal Protein in Cattle Feed

4.1. Introduction

An updated version of the previous EFSA QRA model has been developed specifically to assess the potential infectivity that may be present in manufactured cattle feed due to contamination with Processed Animal Protein (PAP). In the original EFSA QRA Report the residual risk due to MBM was assessed. This new version of the EFSA QRA model will now be referred to as the EFSA QRA PAP model since it only deals with PAPs.

4.2. Model Basis and Structure

4.2.1. Model structure

The EFSA QRA PAP model has been developed from “BSE infectivity model cattle exposure v7” the final version of the EFSA QRA model. The model now consists of four Excel worksheets. The model has been evaluated using @RISK 4.5.5, and run using Latin Hypercube sampling with 10,000 iterations. The four sheets are summarised in the Table 2 here below.

Table 2: Summary on the information provided in the 4 sheets of the “EFSA QRA PAP model” Excel worksheet

Sheet	Description
1-Input data	This sheet includes all the data used for this calculation. There are 3 Run Options that the user must select: 1: Choice of BSE Prevalence Data: Default data for EU27 in 2009 is included. Or the user may specify BSE test data and related data on numbers of cattle slaughtered for any specified country or region. 2: Rendering method: Atmospheric or Pressurised steam 3: Batch or Continuous rendering process
2-PAP to cattle	The sheet provides the calculation of exposure to individual cattle for assumed levels of contamination with PAP. Results given as Infectivity per animal per year.
3-Total exposure	This sheet provides the calculation of the total exposure to BSE infectivity for all cattle in the EU due to consumption of ruminant feed. Results given as total Infectivity per year.
4-Summary Results	This sheet copies the results from Sheet 2 and enables sets of runs (e.g. sensitivity cases) to be generated and compared easily.

The EFSA QRA PAP model is provided as an Annex to this opinion and can be found at the following URL: www.efsa.europa.eu/en/biohazscdocs/docs/efsaqrapapmodel.xls. Moreover, detailed technical information, including information on uncertainties on the model can be found in Appendix II to this opinion.

4.2.2. Model basis

In the event that there were to be some relaxation in the use of non-ruminant PAP in animal feeds (e.g., feeding porcine PAP to poultry) there would be some increase in the risk that ruminant feeds could be contaminated with such material. Non-ruminant PAP should not represent any TSE risk to ruminants as such, but there would be a possibility that the non-ruminant PAP could itself be contaminated with ruminant PAP. The purpose of the model is to estimate the potential exposure of cattle to BSE infectivity due to the potential for contamination of cattle feed with non-ruminant PAP that could include bovine material with traces of infective material.

There are three stages in the model calculation:

1. Calculation of BSE infectivity in ruminant PAP (due to incomplete removal of SRMs);
2. Infectivity in non-ruminant PAP assuming contamination with ruminant PAP;
3. Infectivity in Cattle feed, assuming contamination with non-ruminant PAP (from step 2).

Model results are given in terms of the annual exposure of cattle to BSE infectivity (Cattle oral ID₅₀ units) for two alternative feeding regimes (Intensive and Extensive) and for three levels of contamination of the ruminant feed.

4.2.3. BSE infectivity in Ruminant PAP

Category 1 waste, which is the material including SRM, is separated and disposed of separately in dedicated plants. This material must be completely disposed of by incineration or landfill following heat treatment.

Category 3 ABPs from ruminants may be rendered and the resulting protein material (PAP) used in products such as pet food. This assessment will assume that the starting point is the production of PAP from Category 3 waste that is made from by-products from a mixture of ruminant species that have been slaughtered for human consumption. However, it is an assumption for the opinion that this Category 3 material could be contaminated with low levels of bovine SRM.

The infectivity in ruminant PAP is calculated by combining:

- BSE prevalence in cattle population;
- Assumptions on batch size, by-products per animal, PAP yield, proportion of carcasses with contaminated material present and reduction in infectivity due to rendering;
- Amount of BSE infected tissue in the mixture of by-products from contaminated carcasses;
- Infectivity of BSE infected CNS tissues.

The input data used for this model are presented in section 4.3.

4.3. Input data

4.3.1. Prevalence

In the EFSA QRA model, the prevalence of BSE has been assessed in two steps, each one was based on rough estimates because few data and scientific results were available at that time. The first step was related to the prevalence of clinical cases per year in the cattle population, and was simply categorised in 3 categories of countries depending on their risk of BSE assessed through the Geographical BSE Risk categorisation (EFSA, 2007b; SSC, 2002). The second step was to estimate the number of sub-clinical non-detected per detected BSE positives, in order to account for the infectivity of infected animals that were dead or culled before the end of the incubation time. Based on few modelling studies, the rough estimate was 2 to 3 undetectable infected animals entering the food chain per detected cattle.

In this EFSA QRA PAP model, similar two steps are also used but since more accurate estimates, thanks to the active monitoring of BSE and additional modelling studies based on more accurate data are available the categories of previous GBR status of the MS are no longer used.

- Step 1. The prevalence of detectable cases of BSE can be obtained precisely from the comprehensive surveillance implemented since 2001 in the EU 15, later in the other EU member

states. With the surveillance system in force, almost all infected animals that reach the end of the incubation time at the time of death or slaughter are detected, given the high sensitivity of the rapid test and the comprehensive apparatus. Also, it can be postulated that in the coming years, if the control measures of BSE remain the same, the prevalence of BSE in the EU 27 should continue to decrease or at least remain constant, in light with the analysis carried out recently on 7 EU countries (Ducrot et al., 2010). So it seems reasonable to assume that the BSE prevalence in subsequent years will be less than in 2009. The EFSA QRA PAP model is based on the most recent data available on BSE prevalence in healthy and emergency slaughtered and bovine animals showing clinical signs *at ante mortem* inspection, at the EU27 level, those of 2009. It was obtained on animals tested that were older than 30 months (older than 48 in some MS). In 2009, over a total number of 6,406,402 rapid tests performed on the above mentioned three surveillance streams in EU27, 32 animals were found to be positives¹⁶. That leads to an overall detected prevalence in EU27 tested cattle coming from these three surveillance streams in 2009 of 5.00 positive animals per million animals tested. However, any Category 3 ABPs used to produce PAP would be derived from all slaughtered animals, and not just those tested. For EU27 a total of 21,018,709 cattle were slaughtered in 2009¹⁷ giving a detected prevalence in EU27 slaughtered cattle of 1.52 positive animals per million slaughtered.

- Step 2. Estimates of the number of non detected per detected BSE case in cattle have been made using different models. From Durand (1999), it was estimated (Durand, personal communication) that the percentage of infected cattle that can be detected at the time of testing (death or culling) varies from 31% to 40% if the rapid screening test detects infected animals 3 to 9 months before the end of the incubation time. In the pessimistic option (30%), it represents 2.3 non-detected per detected BSE case. Still on French data, Sala et al. (2010) carried out a simulation model of the surveillance and detection of BSE, that shows that 20% of infected animals are detected with the tests; this represents 4 non-detected per detected BSE case. Modelling studies carried out by de Koeijer (personal communication), based on a model on BSE dynamics (de Koeijer, 2007) have shown that 85% of infected animals (considering all ages) remain non-detected because they are culled or dead before the end of the incubation time, which represents 5.7 non-detected per detected case. A similar range of non-detected per detected case was also found in a study of the German BSE surveillance data (Greiner, personal communication). Finally, from back calculation models developed on the UK data (Arnold and Wilesmith, 2003), it has been estimated (Arnold, personal communication) that 15.7% of the infected animals are detected, corresponding to 5.4 non detected per detected case.

Depending on the culling curve of cattle that can vary between countries, as well as on the age at infection and the infection dose that can modify the incubation time (higher dose, lower incubation time), the models show that the number of non-detected per detected BSE case varies, in a range of 2 to 10 in the situations seen above.

However, apart from in a few tissues such as the ileum, infectivity only develops significantly towards the end of the incubation period (see Section 3.3.6.7). This should mean that the relative infectivity in most infected but non detected animals will be much less than in those that are detected and are thus close to the end of their incubation period.

In this assessment the number of non detected BSE infected animals per detected BSE case was assumed to follow a uniform distribution with a range from 2 to 10, the Panel considers this range as being conservative.

¹⁶ Source European Commission TSE monitoring database, last accessed on 16th November 2010.

¹⁷ Source Eurostat (<http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home>)

4.3.2. Yield of by-products per animal

As noted in the EFSA QRA Report, animals will vary in weight and the yield of by-products will vary with the animal size and according to the cutting practices in the slaughterhouse. According to data from industry provided in the context of section III.4 of the EFSA QRA report, it was estimated that when all SRMs including the vertebrae are excluded the yield of by-products would be 167 kg per bovine (EFSA, 2005a). In the current EFSA QRA PAP model this is represented as a normal distribution with a standard deviation of 10% of the mean.

4.3.3. Proportion of ruminant Cat. 3 material of bovine origin

Based on the total weight of the ruminant carcasses produced each year in the EU by species and assuming that the proportion of the weight of a carcass over the total live weight of an animal is the same for bovines, sheep and goats it has been estimated, on the basis of Eurostat data, that bovine Cat 3 material represents 90% of the material used to produce ruminant PAPs. For instance in 2007 the total weight of the bovine carcasses produced in EU27 was 8,203,646 tonnes while for sheep and goats these weights were respectively 1,010,354 and 79,268 tonnes.¹⁸

4.3.4. Batch size

In the EFSA QRA Report it was assumed that the batch sizes for production of tallow and MBM for a mixture of tissues were in a range from 150 to 1000 tonnes based on information about the size of tallow storage tanks. The number of animals required to make up one batch of material was then calculated by dividing the batch size by the assessed average yield of by-product material per bovine slaughtered (as per 4.3.2). The probability of an infected animal being present in a batch was then determined using a Poisson distribution with the Poisson parameter given by the product of the number of cattle in a batch and the BSE prevalence.

Most production processes are now continuous, so the batch size itself is no longer so relevant, although an effective batch size could be based on the size of product storage units. For this assessment a proxy for a continuous process is used utilising 1,000,000 tonnes as batch size for the base case, with the same range of batch sizes as used in the EFSA QRA Report included as a sensitivity case. The main effect of the batch size will be in the chance that there is an infected animal included in a batch.

4.3.5. PAP yield

In section III.6.5 of the EFSA QRA Report the yield of MBM was taken to be 40% (EFSA, 2005a); i.e., 40 kg of MBM would be produced from every 100 kg of by-products processed. This value was based on industry data for Method 1 (see 4.3.10) processing. Updated information from industry sources indicates that the yield for PAP should be 30 to 35%¹⁹. This is modelled as a Uniform distribution.

4.3.6. Probability of SRM incomplete removal and quantity of SRM remaining tissue per animal

In the EU there is strict separation of SRMs and it is not considered credible that this separated material could re-enter the feed chain. For this assessment it is assumed that all bovine SRMs are removed, including the vertebral column, as per EU regulations for older cattle. However, PAP

¹⁸ Source Eurostat, dataset “food_in_pagr2” Slaughtered animals for food production available at the following link: <http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/>.

¹⁹ Information received from the European Fat Processors and Renderers Association on 4th May 2010.

produced from bovine Category 3 by-products, which may for example be used in pet food, may still have a low level of infective material present due to incomplete removal of SRMs. In addition, recent scientific results (Buschmann and Groschup, 2005; Espinosa et al., 2007; Wells et al., 2005) have indicated that the presence of low levels of infectivity may be present in tissues that are not SRM. However, the infectivity levels found with new highly sensitive analytical techniques are 4 or more logs less than the infectivity in CNS tissue. Such low levels of infectivity would not add significantly to the overall load, and can be assumed to be included within the total amount of SRM material remaining as set out below.

The working group that defined the assumptions for the EFSA QRA Report decided that the incomplete removal of SRM in bovine animals used to produce ruminant MBM should be represented by assuming that 10% of animals slaughtered have some level of incomplete removal of SRMs. This was represented by 5% of brain (25g) and the ileum (80g CNS equivalent) giving a total of 105g of CNS equivalent per animal per animal with SRM incomplete removal. With the level of meat inspection and implementation of SRM controls in the EU this is now considered to be a highly pessimistic assumption both in terms of the likelihood and amount of contamination. This was recognised in the EFSA QRA report which stated that these assumptions represented a worst case scenario in a poorly regulated abattoir.

In the absence of data, for this revised model it is assumed that the numbers of animals with incomplete SRM removal be represented by a distribution, with the 10% value as a maximum. This was modelled as a log normal distribution with a 1 percentile value of 0.1% and a 99 percentile of 5%; this gives a mean value of 1% and a 99.9 percentile of about 10%. This was considered to be more representative of the actual situation.

Similarly in the absence of data, the amount of SRM material remaining due to incomplete removal for the purpose of the current model was assumed to be represented by a log normal distribution with mean value of 10g of CNS equivalent infected tissue and a maximum (99 percentile) of 105g.

These assumptions are combined in the EFSA QRA PAP Model with the infectivity level of CNS in an infected animal (see section 4.3.7.2) to give the total infectivity in the Cat 3 ABP from an infected but non-detected animal that is slaughtered for food of 1 Co ID₅₀ with a 95% range of 0.002 to 8. This value can be compared to equivalent estimates from similar models discussed in section 3 (Cummins and Adkin, 2007; de Vos and Heres, 2009). The values are not reported in the same way in the published papers but have been provided directly by the authors.

Adkin reports that, for the version of the VLA model used in 2007 study, the total number of Co ID₅₀ in Cat 3 materials per year per infected animal was a mean of 466 Co ID₅₀ (5th 93.7, 95th 964.3). However, updates to this model in 2010 have considerably reduced this estimate. When considering the removal of vertebral column with all Dorsal Root Ganglia (DRG) for those animals greater than 30 months, thus excluding DRG from category 3 materials, Adkin reports that the mean infectivity per infected animal would be 1 Co ID₅₀ (95th 0.1, 95th 4) from this model. These results are very similar to those reported above for the EFSA QRA PAP model assumptions.

De Vos also confirmed that her model does calculate the infectivity in each infected non-detected bovine both before and after SRM removal. She reports that the mean infectivity per infected non-detected bovine after SRM removal is 19.5 Co ID₅₀, but with a highly skewed distribution with a median value of 3×10^{-3} and a 95th percentile of 132. The tissue infectivity used in the De Vos model is based on that reported by Comer and Huntly (2004) which pre-dated the results from the second stage of the VLA attack rate experiment and gives a mean infectivity about a factor of 10 greater than that used in the EFSA QRA PAP model. If the value reported by De Vos is adjusted to account for the difference in the assumed infectivity distribution the result would be in good agreement with that from the EFSA QRA PAP model.

4.3.7. Infectivity of Bovine Tissues

4.3.7.1. Estimation of the BSE oral infectious dose 50 in cattle

The Veterinary Laboratory Agency (VLA) in the UK has carried out experiments to determine the BSE minimal oral infectious dose in cattle. In this titration experiment groups of 10 calves were each fed 300g, 100g, 10g and 1g of an homogenate made from the brain stems from clinically sick animals.

According to titration in RIII mice the used brain homogenate contained $10^{3.5}$ mouse i.c./i.p. ID₅₀ per g of tissue.

All animals inoculated with 300g and 100g came down with BSE, and 7 out of 10 in both the 10g and 1g trials. The incubation periods for both the 1g and 10g trials were comparable (between 44 – 71 months).

As it was not possible to determine an ID₅₀ dose from this experiment, an extension of this titration experiment was carried out with doses of 1g, 100mg, 10mg and 1mg (Wells et al., 2007). The results show 3 of 5 in the 1g trial group, 7 out of 15 animals in the 100mg group, 1 out of 15 in the 10mg group, and 1 out of 15 in the 1mg group, positive for BSE. Incubation periods for the positive results in both the 1 and 10mg groups were similar to those for the 1 g trial, but two of the animals in the 100mg group had incubation periods in excess of 90 months.

In their study, Wells et al. (2007) report that the ID₅₀ estimate from these experiments is equivalent to 0.20 g of the brain homogenate used (i.e. 5 ID₅₀/g) with a 95% confidence interval of 0.04 – 1.00g. This value also indicates that 1 cattle oral ID₅₀ is approximately equivalent to $10^{2.8}$ mouse i.c./i.p. ID₅₀ in RIII mice.

4.3.7.2. Infectivity in the Brain and spinal cord

From titrations conducted in mice on brain from clinical or clinical suspect cases of BSE, a wide range of titres have been obtained: $10^{2.4}$ – $10^{5.2}$ mouse i.c.or i.c./i.p. ID₅₀/g (Fraser et al., 1992; Taylor et al., 1994). These data were used to estimate the titre at clinical onset and its variability. From this, the mean titre of brain at clinical onset was given by $10^{3.3}$ mouse i.c.or i.c./i.p. ID₅₀/g with standard deviation of $10^{0.58}$ (Arnold et al., 2009). The working group preparing the EFSA QRA report considered that “with higher titres of BSE affected brain the range could extend to 300 ID₅₀/g” (see section III.2 of EFSA, 2005a) and decided to take a precautionary view and assuming that the infectivity titre in brain of a clinically BSE infected bovine follows the following distribution:

Log normal distribution with

- Median (50 percentile): 5 Co ID₅₀/gram
- Higher 99 percentile: 100 Co ID₅₀/gram

For the present assessment this distribution was considered as a reasonable representation of the infectivity level in the CNS of a cattle affected with BSE.

4.3.7.3. Infectivity in the Dorsal root ganglia

In their 2009 paper Arnold et al. (2009) estimated the infectious titre in cervical and thoracic dorsal root ganglia from cattle orally inoculated with 100g brain material at different time points of their incubation. According to this study the titre in the DRG was lower than CNS, with the thoracic and cervical DRG having mean titres approximately 1 and 1.5 log₁₀ mouse i.c./i.p. ID₅₀/g lower than CNS respectively.

4.3.7.4. Infectivity in the Peripheral Nervous System

There have been a number of study reporting detection of infectivity using transgenic PrP bovine mice (Buschmann and Groschup, 2005; Espinosa et al., 2007) or PrP^{Sc} (Iwata et al., 2006) in some peripheral nervous system tissues.

According to the data reported by Buschmann and Groschup (2005) the infectivity could be detected in some but not all nerves samples from a BSE affected animal. In this study the infectivity level in the positive nerves could be estimated to be about 5-6 log₁₀ folds lower than that in the brain from the same animal. These data are consistent with those reported by Espinosa et al., (2007) in different BSE infected animals using another bovine PrP transgenic mouse model. In this study the author report the detection of infectivity in sciatic nerve from 30 and 33 months post exposed cattle, but its absence in animals killed at 20, 24 and 27 months post exposure (n=1 cattle per time point).

Iwata et al. (2006) reported the detection of PrP^{Sc} in some but not all nerves from 2 naturally BSE infected cases (preclinical stage of the disease). On the basis of PrP^{Sc} biochemical detection (Western Blot) it was estimated that the infectivity in the femoral and lumbar nerves of an affected cattle was 1,000 to 1,400 fold less than the PrP^{Sc} amount detected in the spinal cord.

4.3.7.5. Infectivity in non Nervous System tissues

A large range of tissues collected at various stages of the incubation were tested for the presence of BSE infectivity by mouse bioassay (conventional or bovine transgenic) (Arnold et al., 2009; Buschmann and Groschup, 2005; Espinosa et al., 2007). A more limited range of tissues was also tested by intracerebral inoculation into calves (Wells et al., 2005).

The only non nervous tissues shown to harbour consistent infectivity in these experiments are the distal ileum and lingual tonsil.

In the distal ileum infectivity was evidenced as early as 6 months post oral exposure and seems to persist all along the incubation period. The infectious titres in the distal ileum were estimated to range between 10^{-0.06} and 10^{1.94} i.c./i.p. ID₅₀ in RIII mice per gram depending on the age of the individual (Arnold et al., 2009) (i.e. between 1 and 3 log₁₀ fold lower than in the mean level of infectivity found in the brain from BSE affected individuals).

In lingual tonsil, infectivity was detected

- In one out of 5 calves inoculated intracerebrally with a pool of tonsil collected in orally inoculated cattle killed 10 months post exposure (Wells et al., 2005). There were no other positive results for tonsil at subsequent time points of the study (18, 22, 26, 32 and 36 months post exposure).
- In cattle killed at 20 - 24 - 27 - 30 - 33 months (n=1 animal per time point - no younger animal tested) post inoculation in transgenic mice expressing the bovine PrP gene (1/6 mice in each case) (Espinosa et al., 2007).

On the basis of these data, it was estimated (EFSA, 2008) that the infectivity in the tonsil tissue was less than 1 bovine i.c. ID₅₀/g or 10^{-6.5} Co ID₅₀/g.

Finally, detection of minute amounts of infectivity were reported (bioassay in transgenic bovine mice) in one striated muscle sample collected in a BSE affected cattle (Buschmann and Groschup, 2005). The authors failed to detect infectivity in other muscle samples from the same animal. Using another transgenic bovine PrP mouse model other authors failed to detected infectivity in striated muscle samples (one sample per cattle) collected in cattle orally challenged with BSE (100g) and killed at 20 - 24 - 27 - 30 - 33 months (n=1 animal per time point) (Espinosa et al., 2007). These data remain difficult to interpret. In particular, it is unclear if the detected infectivity was associated to nervous

ramifications present in the muscle sample or to striated muscular cells, as reported in other TSE models (Andreoletti et al., 2004; Thomzig et al., 2004).

At the current state of knowledge it cannot be considered that striated muscles cells are harbouring BSE infectivity in cattle.

4.3.7.6. Total infectivity amount in a BSE clinical case

The total infectivity in a clinical case of BSE is summarised in Table 3. The weights of the various tissues are mainly taken from the LFRA and MLC report (LFRA and MLC, 1997) and the infectivity values are as discussed above, with the infectivity for whole brain taken to be 5 Co ID₅₀/g. It can be seen that 90% of the infectivity is associated with central and peripheral nervous system tissues, with about 10% associated with the distal ileum.

Table 3: Infectivity in a Clinical Case of BSE (Co ID₅₀)

Tissue	Weight (Kg/animal)	Infectivity		
		Co ID ₅₀ /g	Co ID ₅₀ /animal	% over the total amount of infectivity
Brain	0.5	5	2500	≈ 65%
Spinal cord	0.2	5	1000	≈ 26%
Dorsal root ganglia	0.03	0.5 – 0.1	3 – 15	< 0.4%
Trigeminal ganglia	0.02	5	100	≈ 2.5%
Lingual Tonsil	0.05 ¹	0.00005	0.0025	< 0.01%
Distal ileum	0.8	0.005 – 0.5	4 – 400	< 0.01- 10%
PNS	0.96 ²	0.00005	0.05	< 0.01%
TOTAL	2.6		3600 - 4000	

1. The LFRA (1997) report gives the total weight of the tonsil as 200g. 50g is an estimate of the weight of the lingual tonsil.
2. Estimate of total PNS weight from Project TS5002. 2008, Veterinary Laboratories Agency, Weybridge, Surrey, UK.

4.3.7.7. Development of the infectivity in tissues through incubation period

In the CNS, a previous analysis of the data from the VLA Pathogenesis experiment for the Over Thirty Months review risk assessment (Comer and Huntly, 2004) resulted in an estimate of a 2 month doubling time. However, a recent re-analysis of the available data (Arnold et al., 2009) indicates that the doubling time of infectivity in the brain from incubating animals may in fact be slightly less than this, with a most likely value of 1.2 and a 95% range of 1.0 to 1.9 months.

Lingual tonsil was shown to be positive in some BSE incubating animals older than 10 months post exposure. There is no apparent modification of the infectivity level during the incubation phase.

With regards to the distal ileum, several studies indicated that after experimental oral exposure of cattle, infectivity in the distal ileum can be detected at 6, 10, 14, 18, 36, 38 and 40 months post exposure (p.e.) From 6–14 months p.e. infectivity showed a rising titre, followed in older animals by a decrease, which is likely to be highly variable between animals (Arnold et al., 2009; Wells et al., 1996; Wells et al., 1994).

4.3.8. Exposure of Cattle Feed to Ruminant PAP

Non-ruminant PAP in itself would not represent a TSE risk to ruminant animals. The risk potential is that by allowing some animal PAPs to be used in some animal feeds then there is a greater chance that ruminant feeds would be contaminated. In order for cattle feed to be contaminated with the BSE agent it would be necessary for two independent contamination events to occur.

Firstly, non-ruminant PAP is contaminated with ruminant PAP (and that the ruminant PAP had been derived from a batch including an animal with BSE). With the separation of rendering facilities and handling required within the EU this is unlikely to occur. However, at the present time the available tests are not able to differentiate species in the processed material. For this opinion it is assumed that this contamination could range from zero to 5% (modelled as a Uniform distribution). 5% contamination of non-ruminant PAP with ruminant PAP was thought to be a rather pessimistic upper estimate of the possible level of such contamination. It was thought that contamination at such a level could occur only in the most unlikely combination of conditions and so would be highly unlikely. However, it was felt that a pessimistic value was justified because of the absence of a test to differentiate species of origin in PAP.

Secondly, ruminant feed is contaminated with non-ruminant PAP. Ruminant feed should contain no animal proteins, and will be routinely tested. A base case test sensitivity of 0.1% - the present threshold of diagnostic sensitivity - will be assumed (i.e. ruminant feed may contain up to 0.1% non-ruminant PAP without being detected), but values of 0.02% and 2% will also be evaluated for comparison with the previous EFSA QRA report.

4.3.9. PAP and Ruminant Feed Production

Data received from the industry²⁰ indicate that the total PAP production in the EU in 2009 was 2.2 million tonnes, as shown below in Table 4, and that the total amount of Cat 3 material of ruminant origin processed in the EU in 2009 was about 3.4 million tonnes²¹.

Table 4: Total PAP production in EU

Product	Production 2009 tonnes	Proportion used in Pet Food
Poultry PAP	372,000	98%
Feather meal	215,000	50%
Porcine PAP	375,000	92%
All other PAP; mixed including ruminant	1,245,000	44%

Data on the total compound feed production in the EU is given on the website of the European Feed Manufacturers' Federation (FEFAC)²². The total compound feed produced for cattle in the EU in 2009 is given as 38,570,000 tonnes.

4.3.10. Reduction in infectivity by processing

In order to process Category 3 materials for the production of PAPs, rendering plants must use one of seven processing methods described in Annex V to Reg. (EC) 1774/2002, where Method 1 represents the most stringent conditions. Method 1 involves strict standards for rendering the material, heating to a core temperature of more than 133°C for at least 20 minutes without interruption at 3 bar pressure. Method 7 does not prescribe any temperature or pressure standards on the processing of raw materials, but does include microbiological criteria based on the final product.

²⁰ Information received from the European Fat Processors and Renderers Association (EFPPA) on 20th October 2010. The data are for the 19 EU member states that are members of EFPPA and only exclude member states with a relatively low production.

²¹ Information provided by EFPPA (Stephen Woodgate, personal communication received on 1st December 2010). The data are for the 19 EU member states that are members of EFPPA and only exclude member states with a relatively low production.

²² www.fefac.org

According to the Annex VII, Chapter II of the current Reg. (EC) 1774/2002 the following methods have to be used according to the different type of material to be processed:

- Method 1 for mammalian material (other than porcine blood and other than materials destined for incineration or petfood);
- Method 1 to 5 and 7 for porcine blood and for mammalian materials destined for incineration or petfood (this derogation implies a special channelling procedure);
- Method 1 to 5 and 7 for non-mammalian material;
- Method 1 to 7 or a microbiologically safe method for fish material.

The effects of each of the seven processing methods on BSE infectivity is not known with the exception of limited experimental data regarding Method 1. Taylor et al. (Taylor et al., 1995) found that rendering BSE contaminated tissues at 133°C for 20 minutes at 3 bar pressure (Method 1) eliminated BSE infectivity from a starting value of $10^{1.7}$ mouse i.c./i.p ID₅₀/g, yielding a 50 fold reduction. However, this experiment was partially compromised by the relatively low starting titre of infectivity in the raw material, which made it difficult to quantify the extent of infectivity reduction at the limits of sensitivity of the mouse assay models used. In studies involving samples spiked with a ten-fold higher quantity of infectivity than that used by Taylor and co-workers, BSE infectivity remained following the rendering process, however reductions of more than 100 to 1000 fold were measured (Schreuder et al., 1998).

Several studies have also been undertaken to investigate the effect of other rendering processes on prions with lower temperatures and/or pressures than Method 1. The studies focused on historical rendering processes in an attempt to understand the factors that may have led to the BSE epidemic. They demonstrated that the processes historically undertaken in GB and the EC had little effect on the infectivity of the BSE or scrapie agent (Taylor and Woodgate, 1997; Taylor et al., 1995).

When Method 1 rendering is used the infectivity reduction by the saturated steam heat/pressure process (133°C and 3 bar for 20 minutes) has been assessed to be between $10^{1.0}$ to $10^{3.0}$ with $10^{2.3}$ as the most likely value. These values are used with a triangular distribution when applied in the EFSA QRA PAP model.

However, with the feed ban in place, most Category 3 material goes into pet food and is processed at atmospheric pressure. This method would have minimal effect on TSE infectivity.

In this opinion it has been assumed that the atmospheric process is used as a base case and there is no infectivity reduction, but the use of Method 1 is also assessed as a sensitivity case in Section 4.4.4.

4.3.11. Consumption of Feed Concentrate

The amounts of feed concentrate used on any farm will depend on the type of cattle and the production or rearing system. The possible range is reflected by assessing the exposure for two alternative production systems for beef cattle; i) an intensive production system in which the cattle are fed an average of 8 kg/day of feed concentrate (Normal distribution with standard deviation of 2 kg/day), and ii) an extensive production system in which the cattle are fed an average of 1.5 kg/day of feed concentrate (Normal distribution with standard deviation of 1 kg/day) (section IV.7.1 of EFSA, 2005a).

4.4. Results of the EFSA QRA PAP model

In this section two different kinds of results are presented:

- Firstly, in terms of overall total infectivity load that could be present in compound feed produced in the EU.
- Secondly, in order to compare the results of this model with the previous EFSA QRA model, the estimated exposure of individual cattle according to three levels of contamination and two feed systems (intensive versus extensive).

In both cases the results are given for three levels of contamination of the ruminant feed with non-ruminant PAP (a base case of 0.1%, plus 0.02% and 2%).

4.4.1. Total infectivity

The starting point is the prevalence of BSE infection in the EU member states as set out in Section 4.3.1. where it was reported that there were 32 BSE positive cases detected with the BSE testing programme in 2009. In addition to the detected cases there would be a number of infected but non-detected animals, which would mainly have lower levels of infectivity present in their tissues than either those detected or a clinical case. It was estimated that the number of infected but non-detected cases would range from 2 to 10 for every detected case. When these animals are slaughtered all the SRMs are removed and destroyed. The estimate of the residual infectivity in the Cat 3 ABP resulting from the 21 million cattle that are slaughtered per year in the EU (and which would include these infected but not detected cases) is 222 Co ID₅₀ (95 % range: 0.3 to 1380).

Some of this Cat 3 ABP is used raw in pet food, but most is rendered to produce a PAP that is also used in pet food. PAP from non-ruminant animals is processed separately, but if it is assumed that up to 5% of the non-ruminant PAP is contaminated with ruminant PAP (section 4.3.8.) then the potential infectivity in the non-ruminant PAP would be 4.9 Co ID₅₀ (95 % range: 0.002 to 33.3) assuming only atmospheric processing of the PAP.

If non-ruminant PAP were allowed in feed for other non-ruminants it would be processed separately from compound feed for ruminants. Nevertheless, it is assumed that the ruminant feed could be contaminated with this non-ruminant feed up to the limit of detection for animal proteins in the feed (0.1%). This would result in an estimated 0.2 Co ID₅₀ (95 percent range 9 x 10⁻⁵ to 1.3) being present in the 38.6 million tonnes of compound feed produced per year in the EU (data for 2009 from FEFAC). These results are given together with the alternative contamination levels in Table 5.

Table 5: Total infectivity in cattle feed produced in the EU

Contamination of ruminant feed with non-ruminant PAP	Cattle oral ID ₅₀ units per year			
	mean	P2.5	P50	P97.5
a) 0.1%	0.2	9 x 10 ⁻⁵	1.4 x 10 ⁻²	1.3
b) 0.02%	0.04	1.9 x 10 ⁻⁵	2.8 x 10 ⁻³	0.3
c) 2%	3.9	1.9 x 10 ⁻³	2.8 x 10 ⁻¹	27

4.4.2. Individual Cattle Exposure

The following section calculates the estimated exposure of cattle from being fed concentrate feed in either an Intensive feed system or an Extensive feed system, and for three levels of dietary exposure of cattle (a base case of 0.1% contamination and sensitivity cases of 0.02% and 2%) with contaminated non-ruminant (0 – 5%) PAP. The base case represents a continuous rendering process operating at atmospheric pressure that will have not reduced the TSE infectivity in the material. Due to time and resource constraints, for this calculation it is assumed that the distribution of the infective material is homogenous. However, considering the industrial process of PAP production and the fact that infectivity that might enter into the production process will be linked to particular individuals (BSE infected cattle) an homogeneous spreading of the infectious load into the final processed PAP is an oversimplification of the reality. A clumped distribution could lead to a higher infectious load – more concentrated - for fewer animals.

Therefore, the results related to individual exposure in this section should be considered with caution.

An initial set of results for the model are presented in Table 6.

The results given are the mean annual exposure in terms of Bovine oral ID₅₀ units per animal in that feed system. In addition to the mean value, the 2.5 percentile (P2.5), the median (P50) and the 97.5 percentile (P97.5) values are also presented to indicate the distribution of the values.

Table 6: Exposure of Cattle to BSE Infectivity through Concentrate Feed assuming a continuous rendering process operating at atmospheric pressure

Contamination of ruminant feed with non-ruminant PAP	Cattle oral ID ₅₀ units per animal per year			
	mean	P2.5	P50	P97.5
Intensive Feed System				
a) 0.1%	1.3 x 10 ⁻⁸	6.8 x 10 ⁻¹²	8.8 x 10 ⁻¹⁰	8.6 x 10 ⁻⁸
b) 0.02%	2.6 x 10 ⁻⁹	1.4 x 10 ⁻¹²	1.8 x 10 ⁻¹⁰	1.7 x 10 ⁻⁸
c) 2%	2.6 x 10 ⁻⁷	1.4 x 10 ⁻¹⁰	1.8 x 10 ⁻⁸	1.7 x 10 ⁻⁶
Extensive Feed System				
a) 0.1%	2.6 x 10 ⁻⁹	8.8 x 10 ⁻¹³	1.5 x 10 ⁻¹⁰	1.6 x 10 ⁻⁸
b) 0.02%	5.1 x 10 ⁻¹⁰	1.8 x 10 ⁻¹³	3.0 x 10 ⁻¹¹	3.2 x 10 ⁻⁹
c) 2%	5.1 x 10 ⁻⁸	1.8 x 10 ⁻¹¹	3.0 x 10 ⁻⁹	3.2 x 10 ⁻⁷

4.4.3. Discussion of results

The results in Table 6 show that the estimated exposure for the assumed contamination levels is very low indeed. The worst case, with atmospheric processing of the ruminant Category 3 waste material and Intensive feeding of cattle, gives a mean annual exposure of only 1.3 x 10⁻⁸ bovine oral ID₅₀ units per animal per year. This is assuming that the non-ruminant PAP could be contaminated with up to 5% of ruminant PAP that had only been processed using atmospheric methods that do not reduce BSE infectivity. This level of contamination with ruminant material is extremely unlikely to occur. The ruminant feed is then assumed to be contaminated with non-ruminant PAP at the limit of detection (0.1%). Feed is routinely tested for the presence of mammalian proteins and batches with positive results are rejected and not allowed to be used for feed.

An exposure of 1.3 x 10⁻⁸ bovine oral ID₅₀ units over a whole year is very unlikely to result in any BSE infection. Even allowing for an uneven distribution of infectivity in the feed these are very low levels indeed. However, the occurrence of a very small number of cases cannot be excluded.

Table 6 also gives results for 0.2 and 2% contamination of the ruminant feed to indicate the range of conceivable values.

In section 4.4.1 the results are given in terms of the total infectivity present in all the ruminant compound feed produced in the EU in one year. This would represent the total exposure to all the cattle in the EU. It is estimated that the mean total exposure for all cattle is 0.1 Co ID₅₀, with a 95 percent range from 9×10^{-5} to 1.3). This suggests that this exposure would result in only 0.2 additional cases of BSE in the EU in one year. With the ongoing decline in the prevalence of infection in EU countries, this risk would decrease further.

In the “Opinion on the Quantitative risk assessment of the animal BSE risk posed by meat and bone meal with respect to residual BSE risk” (EFSA Journal (2005) 257, 1-30) it was reported that exposure to cattle in a GBR III country with reliable surveillance in an intensive feed system and with 0.1% contamination was a mean value of 1.2×10^{-7} Co ID₅₀ per animal per year. This is equivalent to the individual cattle exposure figures given in table 6, i.e., an individual exposure of 1.3×10^{-8} Co ID₅₀ per animal per year. Thus the values reported here are about a factor of 10 lower, reflecting the reduced prevalence of BSE. There were no equivalent values for the total infectivity.

Models can be used to show in a transparent way which and how data were used in representing a situation and making predictions. There are, however, also limitations in the use of models. They rely – like any other scientific research – on the quality of the data used, the model assumptions and the type of model used. In Appendix II, with a detailed description of the model, information is given to judge the quality of the data, which were used for the calculation, indicating for instance the level of uncertainty for certain parameters. Some of the data are from unpublished sources and some are based on expert opinion. The level of uncertainty has to be taken into account when using the model for risk management decisions. Some parameters in this model still have high levels of uncertainty. This particular model is based on a specific scenario (as shown in Figures 1 and 2), which was considered to be acceptable - while data on the level of incomplete removal and contamination were not available - also using the assumptions of previous opinions. Any change of the scenario would require an adaptation of the model. It also requires further surveillance and monitoring to see whether there are any changes in the BSE situation as well as that only Cat. 3 material is entering into PAPs produced from ruminant material.

4.4.4. Sensitivity analysis

Two sensitivity cases have been evaluated to examine the sensitivity to specific assumption in the assessment:

- (a) Processing method for ruminant PAP;
- (b) Batch versus continuous processing of ruminant PAP.

The results for the sensitivity cases are summarised in Table 7. These are only given in terms of the mean value and for one contamination case (0.1 % contamination of ruminant feed with non-ruminant PAP) and are shown with the base case results for ease of comparison.

Table 7: Summary of Sensitivity Case Results (mean values). All results given only for 0.1% contamination of ruminant feed with non-ruminant PAP.

Sensitivity Case	Total Infectivity in EU per year (Co ID ₅₀ units)	Individual Cattle Exposure in Intensive feed system (Co ID ₅₀ units per animal per year)
Base Case (atmospheric pressure processing, continuous process)	0.2	1.3 x 10 ⁻⁸
a) Saturated steam heat/pressure processing	7.8 X 10 ⁻⁴	4.7 x 10 ⁻¹¹
b) Batch processing	0.2	2.6 x 10 ⁻⁸

The first sensitivity case is the same as that for the base case, except that it is assumed that any ruminant Cat.3 ABP is processed using Method 1; the saturated steam heat/pressure process (133°C and 3 bar for 20 minutes). The detailed results have a similar pattern as the base case with the mean values as given in Table 5 a factor of 250 - 270 lower, representing the effect of the rendering process on any infectivity present in the material.

In the second sensitivity case, it is assumed that the ruminant Cat. 3 ABP is processed as a batch case with the range of batch sizes as per the EFSA QRA report, e.g., 150 to 1,000 tonnes. Other assumptions remain as for the base case. This assumption only affects the Individual Cattle exposure calculation with the results for Total Infectivity remaining the same. With batch processing the mean exposure for individual cattle is estimated to be very similar to the continuous case (2.6 x 10⁻⁸ Co ID₅₀ per animal per year as compared with 1.3 x 10⁻⁸ Co ID₅₀ per animal per year for the continuous case) but the distribution of results is rather different. With a limited batch size and low prevalence many batches will have no infected animals included, resulting in zero infectivity. The detailed results show that the infectivity is zero for 97.4% of the batches.

4.5. Model validation and brief consideration on R₀

While the basic internal validity of the model *structure* can be assessed, based on its level of detail and *a priori* knowledge of the BSE-cattle system, the *accuracy* of the model outcomes cannot easily be determined, and in the absence of certain data, the model predictions remain unvalidated. This is because the accuracy is determined by the parameter values, many of which are unknown or known with a high uncertainty and based on assumed (potentially highly variable) distributions. The large number of uncertainties will combine to increase the variance in output (reducing *precision*). But further, the choice of parameter distribution may also reflect a set of specific assumptions, for example ‘worst cases’. The combination of these assumptions is likely to introduce *bias*, and thereby lower *accuracy*. This is not to say that the output is not useful, for example from a decision making point of view it can sometimes be considered a strength if a certain output is maintained below a threshold over a range of worst case scenarios. However it is important that some effort is made to validate the model findings and that the quantitative nature of the exercise does not in itself lend an air of accuracy to the outputs that in truth they do not possess.

One potential avenue to explore for an assessment of the model predictions is to ensure there is a link between the modelling exercise and known epidemiological trends, which provide the richest source of data on the developing (declining) BSE epidemic. The EFSA QRA PAP model is in essence a linear multiplication of a number of parameters representing the feed/cattle system. We can therefore note the average number of ID₅₀ units that ultimately could reach cattle, resulting from a single ID₅₀ unit entering the feed system. When multiplied by 50% and the average number of ID₅₀s expected to result from the average infected cow at slaughter, this will directly give a rough estimate of the basic reproduction ratio, R₀, the expected number of cases caused by the introduction of 1 infected animal. If R₀ is greater than 1, the system is ‘unstable’ and an epidemic will occur. If R₀ is less than one, the

system is ‘stable’ and any outbreak will die out. The smaller the value of R_0 , the quicker the epidemic will die out. The value of R_0 gives a potential yardstick to validate the model predictions against independent data. This is a difficult exercise, since the ‘what if’ scenarios present in the model may not be directly comparable to any real situations. However, the rate of decline in the epidemic in certain well known case studies will be known under a wide range of intervention scenarios. The question can then be asked: is the expected R_0 from the EFSA QRA PAP model at least consistent with the observed data?

Using the model Base Case, the total number of $CoID_{50}$ present in (contaminated) ruminant feed is expected to be 0.2. This can be translated in 0.1 expected infected cattle. This results from approximately 192 cattle and entering the system, harbouring a total of 222 $CoID_{50}$. A rough estimate for the R_0 value is therefore 0.001. This is obtained dividing the number of expected infected cattle (0.1) by the total number of infected cattle potentially entering into the PAP production system.

The flow of $CoID_{50}$ through the system can be illustrated in figure 2.

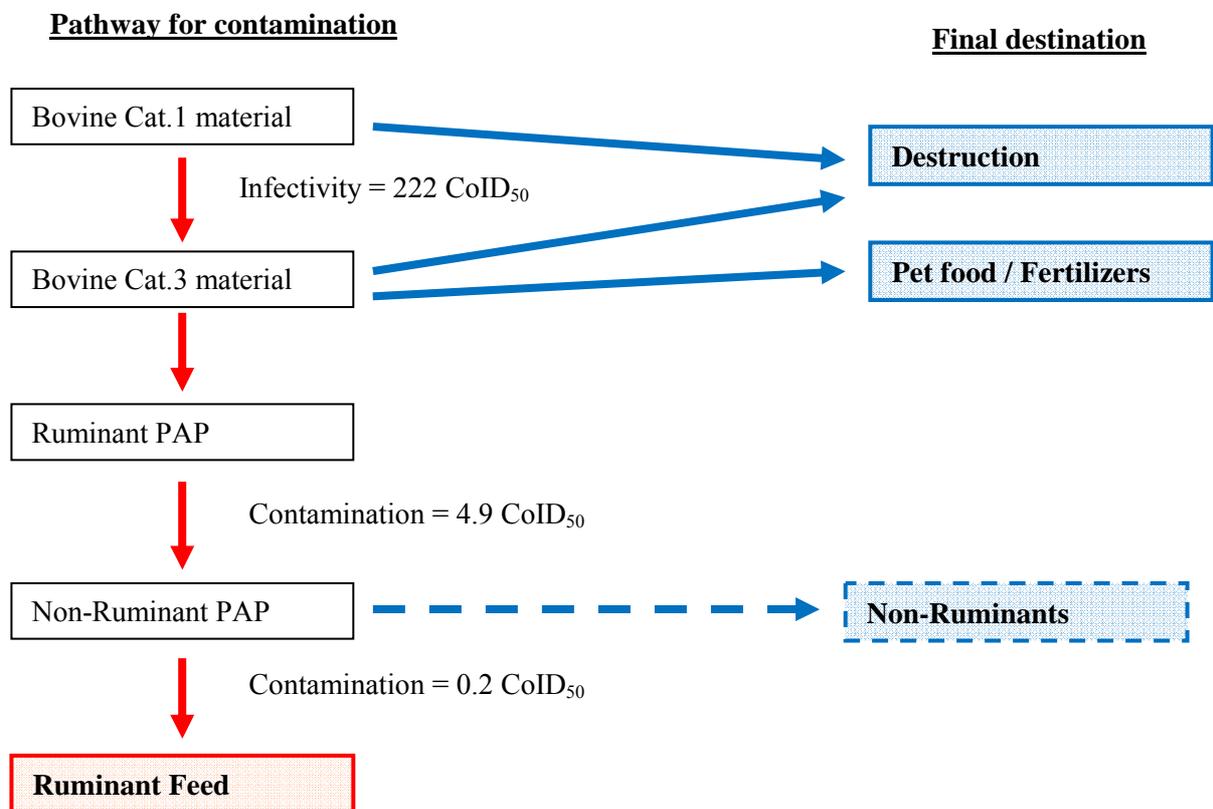


Figure 2: Flow of $CoID_{50}$ through the system. The figures given represent the overall total infectivity load resulting in the different steps of the model. Current and proposed pathways, and potential contamination pathways are as follows:

-  Current legal pathway (not exhaustive)
-  Possible future pathway
-  Contamination pathway

To make a comparison with real data, we examined estimated R_0 values from Europe in the late 1990s (de Koeijer et al., 2004; Ducrot et al., 2010). At this time extended bans were implemented, no ruminant proteins was to be used for any animal feedstuff, and new infections were only likely to arise from contamination. Estimates of R_0 at this time ranged from 0.02 to 0.05. The estimates from the EFSA QRA PAP model therefore suggest a system at least an order of magnitude more stable.

When comparing the EFSA QRA PAP model R_0 value to the data, we note that new cases in the time period considered (known as 'born after the re-enforced ban' (BARB) cases) were, on examination, considered to have resulted from residual contamination or imported feed (Hill, 2005). For example, some feeding units contaminated before the bans (near to the peak of the epidemic) were thought to have remained in use. In the absence of this additional reservoir of infection, we would expect the contamination process represented in the EFSA QRA PAP model to result in a lower risk of transmission of infection, and therefore a considerably lower R_0 . The EFSA QRA PAP approximate R_0 value of 0.001 is roughly an order of magnitude less than the BARB estimates. Although this is only a very rough exercise in model validation, it is concluded that the EFSA QRA PAP model predicts an R_0 value that is consistent with previous epidemiological scenarios, being appropriately lower than that expected from previous BARB cases. The true order of magnitude of the difference cannot be determined, but the output of the model may be considered an upper estimate of risk.

4.5.1. Conclusions

- The EFSA QRA PAP model relies on the continuation of the current SRM policy and TSE monitoring system. It also assumes that only Cat. 3 material is allowed to enter in PAP produced from ruminant material.
- The EFSA QRA PAP model relies on the specific scenario described and on specific assumptions like homogenous mixing. While conservative values are used, uncertainties of certain parameters (i.e. the ratio of detected vs undetected infected animals, the probability of incomplete SRM removal and the amount of infectious tissue remaining after incomplete SRM removal) were identified. Changes in scientific knowledge would require an adjustment of the model.
- The EFSA QRA PAP model calculations are based on the present available data, including unofficial data about PAP production communicated directly by industry. Changes in PAP and feed production would require adjustment of the model input data. The impact of a range of values was assessed by sensitivity analysis.
- Based on 2009 BSE surveillance data and according to the EFSA QRA PAP model, the total BSE infectivity that could be contained into the PAPs produced from ruminants would be equivalent to 222 Co ID₅₀ (0.3 – 1380 CI95%) per year in the whole EU.
- Under the assumption of up to 5% contamination of non-ruminant PAPs with ruminant PAPs the total amount of infectivity that could be present in non-ruminant PAPs would be equivalent to 4.9 Co ID₅₀ (0.002 – 33.3 CI95%) per year in the whole EU.
- Assuming a 0.1% contamination (which is the limit of detection for PAPs in feed) with non-ruminant PAPs, the total BSE infectivity load that could enter in cattle feed in the EU would be equivalent to 0.2 Co ID₅₀ (9×10^{-5} – 1.3 CI95%) (that would mean that less than one additional BSE infected cattle could be expected in the EU cattle population per year with an upper 95% confidence).
- In order to provide a comparison with the earlier EFSA QRA model, a 0.1% contamination (according to the present sensitivity of control measures) and a homogeneous distribution of BSE infectivity into the cattle feed produced in the whole EU was assumed. This would result into an average exposure of cattle to 1.3×10^{-8} Co ID₅₀, which is about 10 times lower than in the earlier

EFSA QRA model, reflecting the reduced prevalence of BSE. Due to uncertainties about the dose-response relation and the real distribution of infectivity in the feed this value does not necessary reflect the individual risk for cattle to be infected with BSE.

- There are few data sets with which to directly validate the model predictions, however the output is broadly consistent (i.e. lower) with the values of R_0 observed during the period after the re-enforced feed ban in the UK and Netherlands.

5. Considerations on Atypical BSE

Systematic testing of cattle over 30 months of age for abnormal prion protein has allowed the identification of two new and distinct types of cattle TSE, termed H-type Atypical BSE (H-BSE) and L-type Atypical BSE (L-BSE or BASE), in a number of European countries (Casalone et al., 2004; Ducrot et al., 2008; Jacobs et al., 2007). Similar cases were also detected outside Europe (Japan and USA) (Clawson et al., 2008; Hagiwara et al., 2007).

In France a retrospective study of all the TSE-positive cattle identified through the compulsory EU surveillance programme between 2001-2007 was performed (Biacabe et al., 2008).

This study indicated that:

- All H- and L-BSE cases detected by rapid tests were observed in animals over 8 years old in either the fallen stock surveillance stream or the abattoir (healthy slaughter).
- No H- and L-BSE were observed in the passive epidemio-surveillance network although, during retrospective interviews, the farmers and veterinarians for 6 of these animals reported clinical signs consistent with TSE in 3 fallen stock.
- Frequency of H- and L- BSE is respectively 0.35 and 0.41 cases per million adult cattle tested but increases to 1.9 and 1.7 cases per million of over 8 years old tested animals.

The number of Atypical BSE cases detected in countries that have already identified them seems to be comparable from year to year. No comprehensive study on the prevalence of Atypical BSE cases has been done in other EU member states and the performances of the currently available rapid test applied for initial TSE screening in the cattle population towards Atypical BSE is still unknown.

The origin of these Atypical BSE cases in cattle is currently unknown as is the performances of the current active surveillance system for detecting H-BSE and L-BSE affected animals resulting in uncertainty about the real prevalence of these conditions.

All Atypical BSE cases identified in EU were born before the extended or real feed ban that came into law in January 2001 (Ducrot et al., 2008). Hence, as with the Classical BSE (C-BSE), exposure of these animals to feed contaminated with low titres of TSE cannot be excluded, although other origins for these TSE forms cannot be discarded. In particular, the unusually old age of all H- and L-type identified cases and their apparent low prevalence in the population could suggest that these Atypical BSE forms are arising spontaneously.

H- and L- BSE have been transmitted to inbred mice and Tg mice expressing bovine and ovine PrP by intra-cerebral challenge. L-BSE has also been transmitted to various models of transgenic mice expressing alleles of the human prion protein (Beringue et al., 2007; Buschmann et al., 2006; Capobianco et al., 2007). More recently the propagation of L-BSE (Fukuda et al., 2009; Lombardi et al., 2008) in cattle through the intracerebral route was reported.

These results indicate that both Atypical BSE agents identified have the potential capacity to propagate in different host species (including cattle).

At this point there is no published information on:

- the transmissibility of Atypical BSE agents in cattle and other species through the oral route;
- the distribution of the infectivity in peripheral tissues and body fluids of cattle with H- and L-BSE;
- the effect of the currently applied TSE agent inactivation process on the H- and L-BSE agents.

Therefore it remains impossible to assess the risk of transmitting a TSE by the mean of PAP that would derive from an Atypical BSE case.

Transmission and serial passage in inbred mice and Tg VRQ mice have been interpreted to indicate that, after interspecies passage, L-BSE could generate C-BSE (Beringue et al., 2007; Capobianco et al., 2007). However, it should be noted that L-BSE : C-BSE phenotypic convergence has not observed in other Tg mice, including mice expressing the ARQ allele of sheep PrP (Beringue et al., 2007; Buschmann et al., 2006).

More recently transmission of H-BSE isolates originating from France and Poland in Tg Bov was reported (Espinosa et al., 2010). While in the majority of the cases the propagated TSE was different from Classical BSE, Classical BSE have emerged in a proportion of the inoculated mice inoculated with two distinct isolates (one from France and one from Poland).

Together these data indicate that the possibility that Atypical BSE might be a source of Classical BSE should be considered with appropriate attention.

5.1. Conclusions on Atypical BSE

- Data are lacking concerning the pathogenesis, the origin (spontaneous disorder/ contagious origin), the detection performances of the TSE epidemiosurveillance system, the true prevalence and the ability of Atypical BSE agents to be transmitted in cattle and other species after oral exposure.
- Some preliminary results seem to indicate that Atypical BSE infected individual could be a potential source of Classical BSE agent.
- There are no data on the effect of the rendering process on the H- and L- BSE infectivity level.
- In this context, the risk of Atypical BSE transmission through PAPs cannot be assessed but should not be disregarded.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- The current global limit of detection for PAPs in feed is still considered to be 0.1%.
- The EFSA 2004 QRA model was reviewed and compared with other published similar risk assessments. The structure of the model is considered to be still suitable for purpose of assessing the residual exposure from Classical BSE for cattle posed by bovine derived processed animal proteins at European Union level.
- For more specific questions and questions concerning particular countries, a more specific or different model should be considered.
- An updated version of the EFSA 2004 QRA model was developed (called EFSA QRA PAP model) to answer the specific terms of reference of this mandate.
- Scientific input data were reviewed and updated. Certain parameters were considered to be conservative and uncertainties were identified.
- The EFSA QRA PAP model relies on the continuation of the current SRM policy and TSE monitoring system. It also assumes that only Category 3 Animal By-Product material is allowed to enter in PAP produced from ruminant material.
- The EFSA QRA PAP model relies on the specific scenario described and on specific assumptions like homogenous mixing. While conservative values are used, uncertainties of certain parameters (i.e. the ratio of detected vs undetected infected animals, the probability of incomplete SRM removal and the amount of infectious tissue remaining after incomplete SRM removal) were identified. Changes in scientific knowledge would require an adjustment of the model.
- The EFSA QRA PAP model calculations are based on the present available data, including unofficial data about PAP production communicated directly by industry. Changes in PAP and feed production would require adjustment of the model input data.
- Based on 2009 BSE surveillance data and according to the EFSA QRA PAP model, assuming a 0.1% contamination (which is the limit of detection for PAPs in feed) with non-ruminant PAPs, the total BSE infectivity load that could enter in cattle feed in the EU would be equivalent to 0.2 Co ID₅₀ ($9 \times 10^{-5} - 1.3$ CI95%) (that would mean that less than one additional BSE infected cattle could be expected in the EU cattle population per year with an upper 95% confidence).
- Considering the many uncertainties related to Atypical BSE L and H (prevalence, tissue distribution of the infectious agent, efficacy of rendering process for agent inactivation) the risk of Atypical BSE transmission through PAPs cannot be assessed. It should however not be disregarded.

RECOMMENDATIONS

- In order to improve the limit of detection of animal proteins in feed the development of analytical methods should be continued.
- Considering the limitations of the model (including the scenario and the uncertainties), if the use of some mammalian PAPs for feeding animals should be reintroduced the risk of (re-)emergence of TSEs in cattle should be taken into account.

- In case of modification of the mitigation measures against BSE this assessment should be updated. The most important measures that were assumed in the EFSA QRA PAP model are the removal of SRMs and strict separation of ruminant and non-ruminant sources in the production and distribution of PAPs.
- Specific data related to the PAP production system and their distribution and use should be collected.
- Specific knowledge related to Atypical BSE should be expanded. In particular with regard to its prevalence, pathogenesis in natural host, capacity to propagate in other animal species and resistance to inactivation processes applied in rendering plants.
- When appropriate information on Atypical BSE will be available the present assessment should be revised.

DOCUMENTATION PROVIDED TO EFSA

1. Letter (ref. n. SANCO/E.2/ZH/rz-D(2009) 520761 dated 11/12/2009) from the European Commission with a request for review and up-date of the scientific data, methodology and review of the quantitative risk assessment (QM) of the residual BSF: risk in mammalian derived meat and bone meal.
2. Opinion of the (EFSA) Scientific Panel on Biological Hazards (BIOHAZ) on the “Quantitative risk assessment of the animal BSE risk posed by meat and bone meal with respect to the residual BSE risk” (Question number: EFSA-Q-2003-099 from 12 July 2005)
3. EFSA QRA Report 2004 (BIOHAZ) on quantitative assessment of the residual BSE risk in Bovine-derived products
4. Third interim report on the Quantitative assessment of the residual BSE risk in bovine – derived products – gelatine, tallow and dicalcium phosphate from bones, tallow from fat tissues, tallow from rendered mixtures of tissues and meat and bone meal ("Dormont & comp. study", 2004)
5. Scientific report on the safety of MBM derived from mammalian animals fed to non-ruminant food-producing farm animals, SSC of 24-25 September 1998.

REFERENCES

- Abbas O, Fernandez Pierna JA, Boix A, von Holst C, Dardenne P and Baeten V, 2010. Key parameters for the development of a NIR microscopic method for the quantification of processed by-products of animal origin in compound feedingstuffs. *Anal Bioanal Chem*, 397, 1965-1973.
- Andreoletti O, Simon S, Lacroux C, Morel N, Tabouret G, Chabert A, Lugan S, Corbiere F, Ferre P, Foucras G, Laude H, Eychenne F, Grassi J and Schelcher F, 2004. PrPSc accumulation in myocytes from sheep incubating natural scrapie. *Nat Med*, 10, 591-593.
- Arnold M and Wilesmith J, 2003. Modelling studies on bovine spongiform encephalopathy occurrence to assist in the review of the over 30 months rule in Great Britain. *Proc Biol Sci*, 270, 2141-2145.
- Arnold ME, Hawkins SA, Green R, Dexter I and Wells GA, 2009. Pathogenesis of experimental bovine spongiform encephalopathy (BSE): estimation of tissue infectivity according to incubation period. *Vet Res*, 40, 8.
- Beringue V, Andreoletti O, Le Dur A, Essalmani R, Vilotte JL, Lacroux C, Reine F, Herzog L, Biacabe AG, Baron T, Caramelli M, Casalone C and Laude H, 2007. A bovine prion acquires an epidemic bovine spongiform encephalopathy strain-like phenotype on interspecies transmission. *J Neurosci*, 27, 6965-6971.
- Biacabe AG, Morignat E, Vulin J, Calavas D and Baron TG, 2008. Atypical bovine spongiform encephalopathies, France, 2001-2007. *Emerg Infect Dis*, 14, 298-300.
- Buschmann A, Gretschel A, Biacabe AG, Schiebel K, Corona C, Hoffmann C, Eiden M, Baron T, Casalone C and Groschup MH, 2006. Atypical BSE in Germany--proof of transmissibility and biochemical characterization. *Vet Microbiol*, 117, 103-116.
- Buschmann A and Groschup MH, 2005. Highly bovine spongiform encephalopathy-sensitive transgenic mice confirm the essential restriction of infectivity to the nervous system in clinically diseased cattle. *J Infect Dis*, 192, 934-942.
- Capobianco R, Casalone C, Suardi S, Mangieri M, Miccolo C, Limido L, Catania M, Rossi G, Di Fede G, Giaccone G, Bruzzone MG, Minati L, Corona C, Acutis P, Gelmetti D, Lombardi G, Groschup MH, Buschmann A, Zanusso G, Monaco S, Caramelli M and Tagliavini F, 2007. Conversion of the BASE prion strain into the BSE strain: the origin of BSE? *PLoS Pathog*, 3, e31.
- Casalone C, Zanusso G, Acutis P, Ferrari S, Capucci L, Tagliavini F, Monaco S and Caramelli M, 2004. Identification of a second bovine amyloidotic spongiform encephalopathy: molecular similarities with sporadic Creutzfeldt-Jakob disease. *Proc Natl Acad Sci U S A*, 101, 3065-3070.
- Clawson ML, Richt JA, Baron T, Biacabe AG, Czub S, Heaton MP, Smith TP and Laegreid WW, 2008. Association of a bovine prion gene haplotype with atypical BSE. *PLoS ONE*, 3, e1830.
- Comer PJ and Huntly PJ, 2004. Exposure of the human population to BSE infectivity over the course of the BSE epidemic in Great Britain and the impact of changes to the Over Thirty Month Rule. *Journal of Risk Research*, 7, 523-543.
- Cummins E and Adkin A, 2007. Exposure assessment of TSEs from the landspreading of meat and bone meal. *Risk Anal*, 27, 1179-1202.
- de Koeijer A, Heesterbeek H, Schreuder B, Oberthur R, Wilesmith J, van Roermund H and de Jong M, 2004. Quantifying BSE control by calculating the basic reproduction ratio R-0 for the infection among cattle. *Journal of Mathematical Biology*, 48, 1-22.
- de Koeijer AA, 2007. Analyzing BSE transmission to quantify regional risk. *Risk Analysis*, 27, 1095-1103.

- de Vos CJ and Heres L, 2009. The BSE risk of processing meat and bone meal in nonruminant feed: a quantitative assessment for the Netherlands. *Risk Anal*, 29, 541-557.
- Ducrot C, Arnold M, de Koeijer A, Heim D and Calavas D, 2008. Review on the epidemiology and dynamics of BSE epidemics. *Vet Res*, 39, 15.
- Ducrot C, Sala C, Ru G, de Koeijer A, Sheridan H, Saegerman C, Selhorst T, Arnold M, Polak MP and Calavas D, 2010. Modelling BSE trend over time in Europe, a risk assessment perspective. *Eur J Epidemiol*, 25, 411-419.
- Durand B, Calavas D, Philippe S and Ducrot C, 1999. Model of BSE dynamics in infected French herds. *Epidemiologie et Sante Animale*, 111-122.
- EFSA (European Food Safety Authority), 2005a. EFSA QRA Report 2004 on quantitative assessment of the residual BSE Risk in bovine-derived products. *The EFSA Journal*, 307, 1-135.
- EFSA (European Food Safety Authority), 2005b. Opinion on the Quantitative risk assessment of the animal BSE risk posed by meat and bone meal with respect to the residual BSE risk. *The EFSA Journal*, 257, 1-30.
- EFSA (European Food Safety Authority), 2007a. Certain Aspects related to the Feeding of Animal Proteins to Farm Animals. *The EFSA Journal*, 576, 1-41.
- EFSA (European Food Safety Authority), 2007b. Opinion of the Scientific Panel on Biological Hazards on the revision of the Geographical BSE risk assessment (GBR) methodology. *The EFSA Journal*, 463, 1-35.
- EFSA (European Food Safety Authority), 2008. Consumption of beef tongue: Human BSE risk associated with exposure to lymphoid tissue in bovine tongue in consideration of new research findings - Scientific Opinion of the Panel on Biological Hazards *The EFSA Journal*,
- Espinosa JC, Andreoletti O, Lacroux C, Prieto I, Lorenzo P, Larska M, Baron T and Torres JM, 2010. Atypical H-type BSE Infection in Bovine-PrP Transgenic Mice Let to the Emergence of Classical BSE Strain Features. *Prion2010*, Salzburg, 137.
- Espinosa JC, Morales M, Castilla J, Rogers M and Torres JM, 2007. Progression of prion infectivity in asymptomatic cattle after oral bovine spongiform encephalopathy challenge. *J Gen Virol*, 88, 1379-1383.
- Fraser H, Bruce ME, Chree A, McConnell I and Wells GA, 1992. Transmission of bovine spongiform encephalopathy and scrapie to mice. *J Gen Virol*, 73 (Pt 8), 1891-1897.
- Fukuda S, Iwamaru Y, Imamura M, Masujin K, Shimizu Y, Matsuura Y, Shu Y, Kurachi M, Kasai K, Murayama Y, Onoe S, Hagiwara K, Sata T, Mohri S, Yokoyama T and Okada H, 2009. Intraspecies transmission of L-type-like Bovine Spongiform Encephalopathy detected in Japan. *Microbiol Immunol*, 53, 704-707.
- Fumiere O, Marien A, Pierna JAF, Baeten V and Berben G, 2010. Development of a real-time PCR protocol for the species origin confirmation of isolated animal particles detected by NIRM. *Food Additives and Contaminants Part a-Chemistry Analysis Control Exposure & Risk Assessment*, 27, 1118-1127.
- Fumiere O, Veys P, Boix A, von Holst C, Baeten V and Berben G, 2009. Methods of detection, species identification and quantification of processed animal proteins in feedingstuffs. *Biotechnologie Agronomie Societe Et Environnement*, 13, 59-70.
- Hagiwara K, Yamakawa Y, Sato Y, Nakamura Y, Tobiume M, Shinagawa M and Sata T, 2007. Accumulation of mono-glycosylated form-rich, plaque-forming PrP^{Sc} in the second atypical bovine spongiform encephalopathy case in Japan. *Jpn J Infect Dis*, 60, 305-308.
- Hill WG, 2005. Review of the Evidence for the occurrence of Bovine Spongiform Encephalopathy cases born after July 1996.

- Iwata N, Sato Y, Higuchi Y, Nohtomi K, Nagata N, Hasegawa H, Tobiume M, Nakamura Y, Hagiwara K, Furuoka H, Horiuchi M, Yamakawa Y and Sata T, 2006. Distribution of PrP(Sc) in cattle with bovine spongiform encephalopathy slaughtered at abattoirs in Japan. *Jpn J Infect Dis*, 59, 100-107.
- Jacobs JG, Langeveld JP, Biacabe AG, Acutis PL, Polak MP, Gavier-Widen D, Buschmann A, Caramelli M, Casalone C, Mazza M, Groschup M, Erkens JH, Davidse A, van Zijderveld FG and Baron T, 2007. Molecular discrimination of atypical bovine spongiform encephalopathy strains from a geographical region spanning a wide area in Europe. *J Clin Microbiol*, 45, 1821-1829.
- LFRA and MLC (Leatherhood Food Research Association and Meat & Livestock Commission), 1997. Audit of bovine and ovine slaughter and by-products sector (ruminant products audit). Carried out by Hart, R.J., Kempster, A.J., *et al*, for the UK Ministry of Agriculture, Fisheries and Food (MAFF). 42.
- Lombardi G, Casalone C, A DA, Gelmetti D, Torcoli G, Barbieri I, Corona C, Fasoli E, Farinazzo A, Fiorini M, Gelati M, Iulini B, Tagliavini F, Ferrari S, Caramelli M, Monaco S, Capucci L and Zanusso G, 2008. Intraspecies transmission of BSE induces clinical dullness and amyotrophic changes. *PLoS Pathog*, 4, e1000075.
- Prado M, Berben G, Fumiere O, van Duijn G, Mensinga-Kruize J, Reaney S, Boix A and von Holst C, 2007. Detection of ruminant meat and bone meals in animal feed by real-time polymerase chain reaction: Result of an interlaboratory study. *Journal of Agricultural and Food Chemistry*, 55, 7495-7501.
- Sala C, Durand B and Calavas D, 2010. Evaluation de la performance de la surveillance exhaustive de l'ESB en France. Approche par simulation. Paris.
- Schreuder BE, Geertsma RE, van Keulen LJ, van Asten JA, Enthoven P, Oberthur RC, de Koeijer AA and Osterhaus AD, 1998. Studies on the efficacy of hyperbaric rendering procedures in inactivating bovine spongiform encephalopathy (BSE) and scrapie agents. *Vet Rec*, 142, 474-480.
- SSC (Scientific Steering Committee), 1998. Report and Scientific Opinion on mammalian derived meat and bone meal forming a cross-contaminant of animal feedstuffs adopted by the Scientific Steering Committee at its meeting of 24-25 September 1998.
- SSC (Scientific Steering Committee), 2002. Opinion of the Scientific Steering Committee on the Geographical BSE-Risk (GBR) and its evolution over time in the European Union Member States. 1-4.
- Taylor DM, Fraser H, McConnell I, Brown DA, Brown KL, Lamza KA and Smith GR, 1994. Decontamination studies with the agents of bovine spongiform encephalopathy and scrapie. *Arch Virol*, 139, 313-326.
- Taylor DM and Woodgate SL, 1997. Bovine spongiform encephalopathy: the causal role of ruminant-derived protein in cattle diets. *Rev Sci Tech*, 16, 187-198.
- Taylor DM, Woodgate SL and Atkinson MJ, 1995. Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. *Vet Rec*, 137, 605-610.
- Thomzig A, Schulz-Schaeffer W, Kratzel C, Mai J and Beekes M, 2004. Preclinical deposition of pathological prion protein PrPSc in muscles of hamsters orally exposed to scrapie. *J Clin Invest*, 113, 1465-1472.
- van der Sluijs JP, Craye M, Funtowicz S, Klopogge P, Ravetz J and Risbey J, 2005. Combining quantitative and qualitative measures of uncertainty in model-based environmental assessment: the NUSAP system. *Risk Anal*, 25, 481-492.
- Veys P and Baeten V, 2010. New approach for the quantification of processed animal proteins in feed using light microscopy. *Food Additives and Contaminants Part a-Chemistry Analysis Control Exposure & Risk Assessment*, 27, 926-934.

- von Holst C, Baeten V, Boix A, Slowikowski B, Pierna JAF, Tirendi S and Dardenne P, 2008. Transferability study of a near-infrared microscopic method for the detection of banned meat and bone meal in feedingstuffs. *Analytical and Bioanalytical Chemistry*, 392, 313-317.
- Wells GA, Dawson M, Hawkins SA, Green R, Dexter I and Francis ME, 1996. Preliminary Observations on the pathogenesis of experimental bovine spongiform encephalopathy. In: *Bovine spongiform encephalopathy: The BSE Dilemma*. CJ Gibbs. Springer-Verlag, New York, 28-44.
- Wells GA, Dawson M, Hawkins SA, Green RB, Dexter I, Francis ME, Simmons MM, Austin AR and Horigan MW, 1994. Infectivity in the ileum of cattle challenged orally with bovine spongiform encephalopathy. *Vet Rec*, 135, 40-41.
- Wells GA, Konold T, Arnold ME, Austin AR, Hawkins SA, Stack M, Simmons MM, Lee YH, Gavier-Widen D, Dawson M and Wilesmith JW, 2007. Bovine spongiform encephalopathy: the effect of oral exposure dose on attack rate and incubation period in cattle. *J Gen Virol*, 88, 1363-1373.
- Wells GA, Spiropoulos J, Hawkins SA and Ryder SJ, 2005. Pathogenesis of experimental bovine spongiform encephalopathy: preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle. *Vet Rec*, 156, 401-407.
- WHO (World Health Organisation), 2008. Harmonization project document no. 6: Part 1: Guidance document on characterizing and communicating uncertainty in exposure assessment. Harmonisation Project Document Series,
- WHO (World Health Organisation), 2009. Risk Characterization of Microbiological Hazards in Food: Guidelines. Microbiological Risk Assessment Series, 17,
- Yamamoto T, Tsutsui T, Nonaka T, Kobayashi S, Nishiguchi A and Yamane I, 2006. A quantitative assessment of the risk of exposure to bovine spongiform encephalopathy meal via meat-and-bone in Japan. *Preventive Veterinary Medicine*, 75, 221-238.

A. APPENDIX I: COMPARISON OF THE KEY PARAMETERS AND COMPONENTS IN FOUR MBM RISK ASSESSMENTS

Parameter description	Risk assessment			
	EFSA QRA	Yamamoto et al., 2006	De Vos and Heres, 2009	Cummins and Adkin, 2007
Country/region	Europe wide. Based on old Geographical BSE Risk Assessment categories	Overall risk estimated for Japan, but regional estimates also considered with no movement of MBM between regions (i.e. MBM produced per region consumed within that region)	Netherlands	UK and Ireland, UK model explored here
MBM specification	MBM produced from a mixture of tissues. Assumed to be 40% bovine. 3 alternative options considered for removal of SRM -No SRM removed -SRM removed except vertebral column -All SRM removed	None	Category 3: derived from animals prepared fit for consumption, SRM and testing controls applied	Category 3: derived from animals prepared fit for consumption, SRM and testing controls applied
Number of infected animals	Varies with GBR Status Number per million clinical (mode; range) GBR II (0.5; 0-1) GBR III (30; 1-99) GBR IV (300; 100-1000) Plus number undetected pre-clinical GBR II (3; 2-4) GBR III (100; 2-400) GBR IV (1000; 200-4000)	One infected undetected cow (either dead on farm or fit for consumption)	One infected cow slaughtered for consumption	Number of infected, undetected cattle slaughtered for consumption and in the last 12 months of incubation period, mean 0.3
Detection of infected animals	100% clinical cases detected if reliable surveillance; none detected if unreliable	Not detected	Dependent on months before clinical onset, detection limit of test (visual or laboratory), and infectivity titre in CNS	Not detected

Parameter description		Risk assessment			
		EFSA QRA	Yamamoto et al., 2006	De Vos and Heres, 2009	Cummins and Adkin, 2007
Clinical state		Pre-clinical and clinical as above	Clinical	Variable – pre-clinical and clinical	Clinical
Infectivity titre		Median of 5 Co ID ₅₀ /g 99 percentile 100 Co ID ₅₀ /g	10 Co ID ₅₀	Dependent on age at exposure, Dutch incubation period, date at slaughter and doubling time	Variable estimate, mean 10 Co ID ₅₀
Infectious tissues included		CNS (brain, spinal cord, dorsal root ganglia, trigeminal ganglia) 750 g, plus other SRMs at reduced titre	750 g	CNS (brain, spinal cord, dorsal root ganglia, trigeminal ganglia) mean 750 g, s.d. 50	CNS (brain, spinal cord, dorsal root ganglia)
Infectivity remaining post abattoir controls		Variable	All	Reduction in infectivity remaining based on 2 scenarios, normal procedures, and insufficient removal where 200g of SRM remain	Reduction in infectivity based on failure rates to remove each SRM correctly and contamination caused by carcass splitting and brain embolisms during processing
Rendering method applied		Saturated steam/pressure	Three types, one continuous and two batch processes	Method 1 Annex VII, Chapter II of the current Reg. (EC) 1774/2002	Method 1 Annex VII, Chapter II of the current Reg. (EC) 1774/2002
Infectivity remaining post rendering		Reduction factor: Min: 10 Mode: 200 Max.: 1000	For three types of rendering 1 x 10 ⁻¹ , 1 x 10 ⁻³ and 1 x 10 ⁻¹ reduction respectively	~ 5 x 10 ⁻³	Uncertain, mean 1 x 10 ⁻²
Contamination routes investigated		3 levels of possible MBM contamination in ruminant feed: 0.1%; 0.02% and 2%.	<ul style="list-style-type: none"> • Ruminant feed containing MBM as an ingredient • Ruminant feed contaminated with MBM from non-ruminant feed • Directly feeding MBM in supplements 	<ul style="list-style-type: none"> • Feed Mill • Primary Farm • Pasture contamination through non-ruminant manure fertiliser 	<ul style="list-style-type: none"> • Pasture contamination through fertiliser application
Population exposed		Beef and dairy cattle	Beef and dairy cattle	Dairy cattle and calves	Beef and dairy cattle

Parameter description	Risk assessment			
	EFSA QRA	Yamamoto et al., 2006	De Vos and Heres, 2009	Cummins and Adkin, 2007
Amount consumed	Extensively reared cattle: 1.5 kg feed/day Intensively reared cattle: 8 kg feed/day	Route 1 infectivity homogenously mixed and applied to the number of cattle fed concentrates Route 2 homogenously spread over 10 batches and fed to cattle. Route 3 infectivity homogenously mixed and applied to the number of cattle fed supplements Dependent on the amount consumed.	All infectivity consumed on one or two farms. Dependent on amount of concentrates consumed, number of calves and dairy cows on average Dutch dairy farm	Infectivity spread on farms homogenously based on number of farms using MBM based fertiliser
Dose response	Not included, linear dose response implied.	Not included	Binomial process with probability of infection per ID ₅₀ of 0.5	Not included

B. APPENDIX II: DETAILED DESCRIPTION OF THE EFSA QRA PAP MODEL

This description of the model is based on the format proposed as part of the risk project (ref: <http://www.bfr.bund.de/cd/52162>).

This report is designed to facilitate a detailed review of the model. Section 1 contains a basic description of the model. Section 2 describes a qualitative scoring system for uncertainty and knowledge base. This scheme is used in the same section for assessing general aspects of the model and later-on for assessing model input such as data and parameters. Section 3 contains a detailed description of all model inputs, sorted by the model parts in which they were defined.

In addition to this documentation, the model was also independently implemented and re-calculated with the risk tool. The figures from 4 to 8 of this Appendix have been produced using the risk tool. The model results were confirmed. This provides an additional aspect of model validation (technical verification of the implementation).

1. GENERAL DESCRIPTION OF THE MODEL

1.1. Background

This model is an updated version of a probabilistic model for the residual BSE risk in bovine-derived products (EFSA, 2005a). Further background information can be found in the main document.

1.2. Objectives

The objective of the model is to estimate the residual BSE risk in terms of:

- overall total infectivity load that could be present in compound cattle feed produced in the EU; and
- exposure of individual cattle according to three levels of contamination and two feed (intensive versus extensive) systems.

1.3. Scope

1. The model relies on the continuation of the current risk mitigation measures including removal of SRM and BSE surveillance.
2. The model does not address more specific questions such as modification of mitigation measures or particular country-specific scenarios.
3. The model does not consider the exposure route via fertilizers.
4. The modelling approach is conservative. Uncertain model input quantities have in general been defined using worst-case assumptions. Thus, the resulting risk estimates are expected to be biased to higher values compared with realistic predictions.
5. Many model input parameters are based on expert opinion

1.4. Model concept

The purpose of the model is to evaluate the presence and concentration of BSE infectivity along the processing chain from raw materials to cattle feed. Probabilistic (stochastic) modelling was used to capture variability and uncertainty in model inputs. The model concept is summarised in Fig. 3. The

model is a simplified re-implementation of an EXCEL/@RISK model, which was developed recently (EFSA, 2005a) and has been updated by EFSA (see main report).

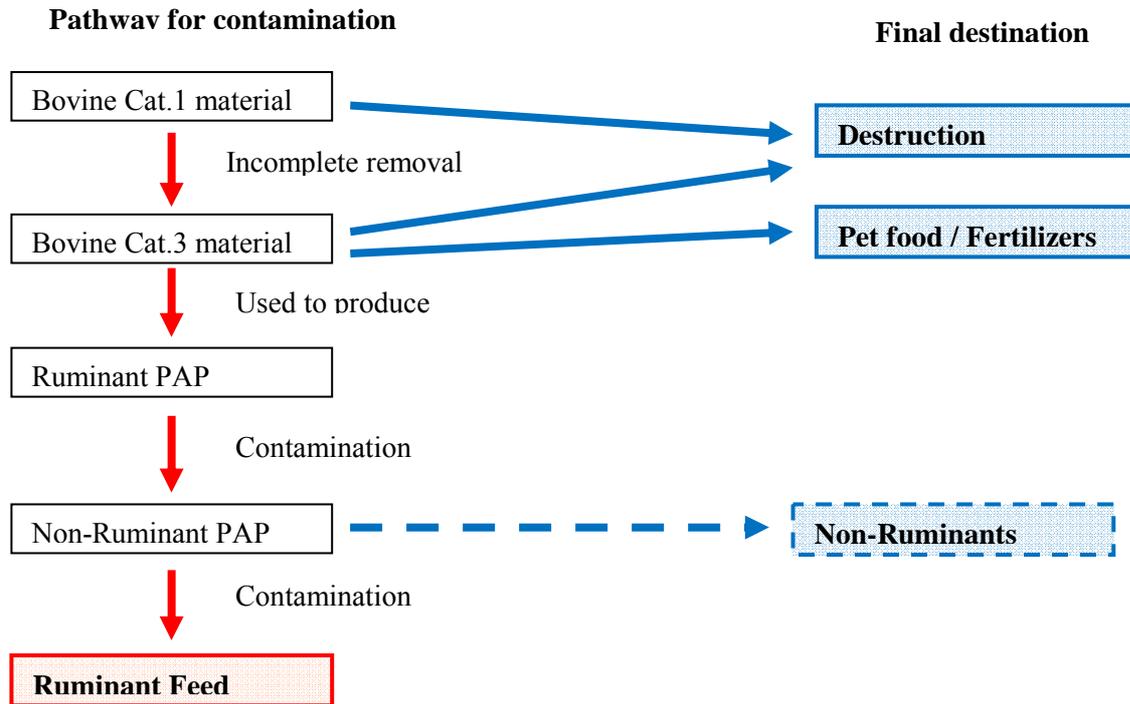
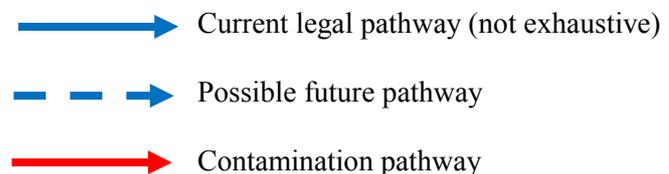


Figure 3: Main pathways of the EFSA QRA PAP Model. The figures given are the assumptions of the model. Current and proposed pathways, and potential contamination pathways are as follows:



2. Model uncertainties and knowledge base

2.1. Qualitative scoring system

Uncertainties and the knowledge base of general aspects of the model have been assessed systematically. Apart from verbal descriptions, a qualitative scoring system has been used (see Tab. 7 and 8). The criteria were plausibility (U1), intersubjectivity (U2), choice space (U3), sensitivity to limitations (U4), sensitivity to interests (U5), influence (U6), proxy (K1), strength of evidence (K2), internal validity (K3) and external validity (K4). Depending on the aspect of the model assessed, either the criteria for expressing uncertainty (U) or those expressing knowledge base (K) may be more relevant.

The same scoring scheme was also used to assess model input such as data and parameters (see “Scores” in tables in Section 3).

The score values serve only the purpose of illustration and are not used in any calculation.

When in the scoring system the value of 0 has been used that means the specific criterion was not applicable.

Table 8: Default criteria and qualitative scores for uncertainty (i.e. assumptions considered) (modified from van der Sluijs et al., 2005)

Criterion	Scores and definitions (interpretation guide)
(U1) Plausibility	1=high (highly plausible despite absence of factual evidence), 2=medium (plausible despite absence of factual evidence), 3=low (plausibility questionable or not assessed; fictive or speculative assertion)
(U2) Inter-subjectivity	1=high (expert opinions are consistent among peers), 2=medium (expert opinions vary among peers to some extent; deviating minority opinions exist), 3=low (expert opinions vary considerably among peers; no clear majority opinion exists)
(U3) Choice space	1=limited (hardly any choice from alternative assumptions), 2=moderately limited (limited choice from alternative assumptions), 3=wide (ample choice from alternative assumptions)
(U4) Sensitivity to limitations	1=hardly sensitive (more resources such as time, money, etc. would not markedly reduce the uncertainty), 2=moderately sensitive (more resources would markedly reduce the uncertainty), 3=very sensitive (more resources could resolve this aspect of uncertainty)
(U5) Sensitivity to interests*	1=hardly sensitive (assumptions are not related to any interests of the experts), 2=moderately sensitive (assumptions are moderately related to interests), 3=sensitive (assumptions are related to interests)
(U6) Influence	1=low (local effect in the model, few pathways affected), 2=medium (several pathways affected), 3=high (many pathways affected)

* this score has been considered to be 1 for all the elements of the model since the EFSA system for Declaration of Interest avoid the possible conflict of interests.

Table 9: Default criteria and qualitative scores for knowledge base (i.e. data considered) (modified from van der Sluijs et al., 2005)

Criterion	Scores and definitions (interpretation guide)
(K1) Proxy	1=high (exact measure or good fit for purpose), 2=medium (well correlated), 3=low (weak correlation or not clearly correlated)
(K2) Strength of evidence	1=high (strong evidence, systematic review and meta-analysis of suitable studies, official statistics, census data, controlled randomised trial, observational study with appropriate study design and adjustment for confounding), 2=medium (some evidence, like level 1 but constraints of internal or external validity apply), 3=low (no evidence, expert opinion, assumption)
(K3) Internal validity	1=high (internal validity assessed with positive outcome, measurement methods validated and considered best-suited for the purpose), 2=medium (internal validity assessed with acceptable outcome, measurement methods validated and considered acceptable for the purpose), 3=low (internal validity not assessed or assessed with questionable outcome)
(K4) External validity	1=high (external validity for the purpose of this assessment can be presupposed), 2=medium (external validity for the purpose of this assessment can be presupposed with limitations), 3=low (external validity for the purpose of this assessment may not be given)

2.2. Assessment of general model uncertainties

The assessed sources of uncertainty have been proposed in a guidance paper on uncertainty and data quality in exposure assessment (WHO, 2008) and guidelines for risk characterization of microbial hazards in food (WHO, 2009). Two uncertainty aspects mentioned in the latter document were merged here under the subcategory resolution under the main category of model uncertainty.

2.3. Assessment of scenario uncertainty

The following aspects of scenario uncertainty were identified and assessed. Fig. 4 and the score values below summarise the 10 criteria scores for each of the aspects.

- Agents** The BSE agent is the defined hazard as per the risk question. The role of Atypical BSE is elaborated in the main report (see section 5). There is a relevant uncertainty due to a lack of data and knowledge of the epidemiological characteristics of Atypical BSE agent. Classical BSE is currently declining and in future the importance of Atypical BSE on the overall BSE cases may become more important.
 Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
3	1	2	1	1	3	0	0	0	0

- Sources** The source of the hazard is the SRM from BSE infected cattle. We see no important uncertainty related to the sources.
 Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	2	0	0	0	0

- Populations** The European cattle population is target of this assessment. The variability of risk factors such as production system and animal feed production of the European cattle populations were not considered. Therefore, we see the population as a relevant source of uncertainty.
 Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
3	1	3	3	1	1	0	0	0	0

- Microenvironments** A relevant microenvironment issue is given by the processing of PAPs. The inactivation rate of the BSE agent during processing depends on the temperature, pressure and time. The methods are specified in the European legislation. Process control data have not been available. Therefore, a medium level of uncertainty is asserted to the processing of proteins.
 Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
2	1	2	3	2	2	0	0	0	0

- Temporal** Temporal factors were not considered in the model. It can be assumed that the processing of animal proteins has a certain volatility in response to economic factors. However, our model is thought to capture worse-case scenarios and therefore no important uncertainty is attributed to temporal factors.
 Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	2	1	1	1	0	0	0	0

- **Spatial** Raw materials are sourced from different cattle production systems and are processed in systems with considerable variability within the EU. However, our model is thought to capture worse-case scenarios and therefore no important uncertainty is attributed to spatial factors.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	2	1	1	1	0	0	0	0

- **Measures** The removal of SRM is the most important risk measure. We assume compliance with this measure but allow for incomplete removal of SRM that might then enter in Category 3 material. Thus, the model is thought to reflect reality and we see no important uncertainty related to measures. A violation of the assumption would probably have a high impact on the model outcome.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	2	0	0	0	0

- **Activities** We see no relevant component of human behaviours, activities and attitudes to be captured by the model. Therefore, this aspect is not applicable.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
0	0	0	0	0	0	0	0	0	0

- **Pathways** Other BSE infectivity exposure pathways for cattle such as, for example, via fertiliser and pasture (see section 3.1 of main report) may occur and were not included in this model. However, based on the results of these models and due to the focus of the mandate on the feed processing chain, the importance of such pathways in the context of this assessment was found marginal. Within the general scenario pathway for cattle feed, we identified no relevant uncertainty.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	2	0	0	0	0

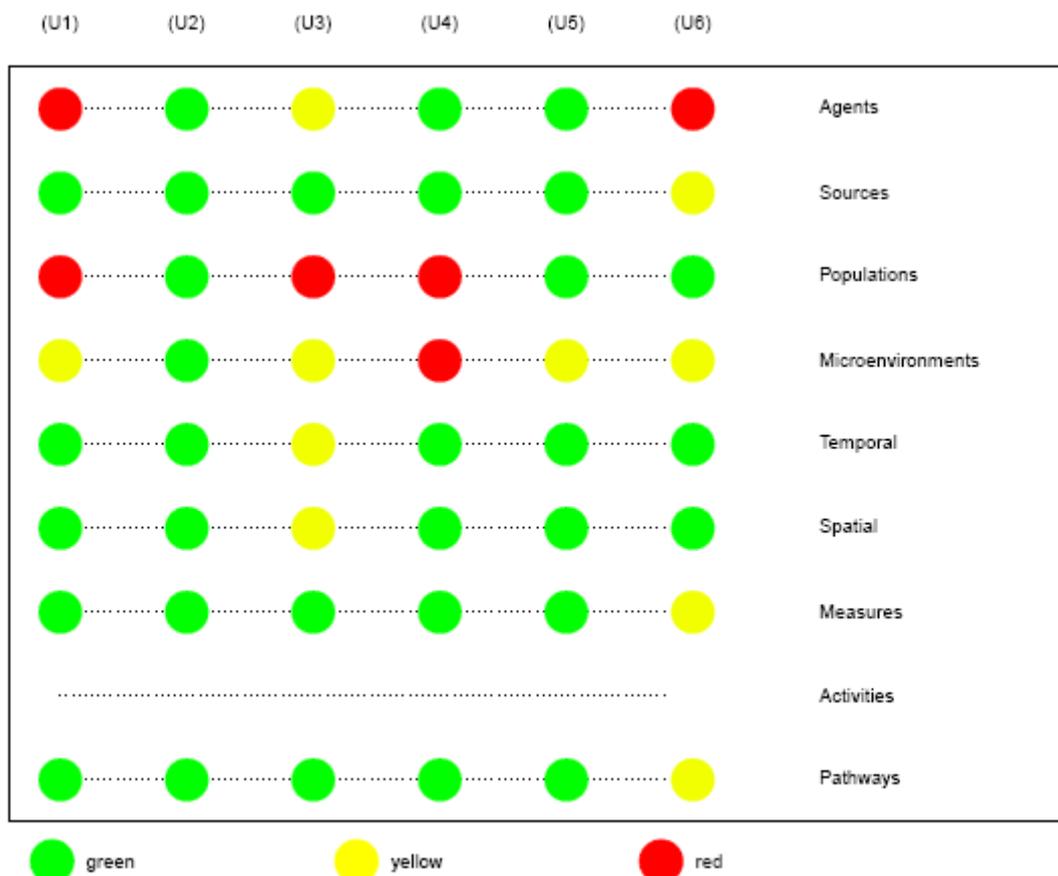


Figure 4: Scoring of scenario uncertainty and knowledge base: plausibility (U1), intersubjectivity (U2), choice space (U3), sensitivity to limitations (U4), sensitivity to interests (U5), influence (U6), proxy (K1), strength of evidence (K2), internal validity (K3) and external validity (K4). The qualitative scores are represented as dots using a traffic light colour scheme to signal low (green), medium (yellow) and high (red) uncertainty. No dots were drawn for criteria that were found not applicable, resulting in omission of columns for some criteria (K1, K2, K3, K4).

2.4. Assessment of modelling approach uncertainty

The following aspects of modelling approach uncertainty were identified and assessed. Fig. 5 and the score values below summarise the 10 criteria scores for each of the aspects.

- Concept** This model is a reflection of the relevant processes that may lead to and modify the BSE infectivity of cattle feed. We are certain about this model concept.
 Scores:

U1U2U3U4U5U6K1K2K3K4
1 1 1 1 1 2 0 0 0 0

- Structure** A low level of uncertainty due to model structure can be asserted under the condition that the chosen model is parsimonious and the parameters can be derived from available data. The lack of data for many important parameters is a limitation but no alternative model could be designed to avoid data-sparse parameters. Therefore, we do not see the model structure as relevant source of uncertainty.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	2	0	0	0	0

- Type** The type of model can be described as probabilistic risk scenario model. It is commonly accepted that this type of model is capable to reflect a known or plausible deterministic model structure as well as variability and uncertainty in model input quantities. We do not attribute the type of model as a source of uncertainty.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	2	0	0	0	0

- Resolution** The level of detail in this model is low. Risk factors that may impact any of the key parameters are not included in the model. We believe that the model will provide average risk estimates for the EU under pessimistic assumptions for uncertainty model inputs. The influential parameters could be more refined or stratified if necessary and if specific data are available. We ascribe a medium level of uncertainty due to the level of detail in this model.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
2	1	3	3	1	2	0	0	0	0

- Dependencies** The distributions of stochastic model input data were assumed as independent. No data or expert opinion was available to estimate the dependency structure. When the dependencies are not accounted for, the simulated outcome function may be biased towards less weight for high-risk scenarios. We propose that the current model contains no critically dependent input parameters and that the uncertainty related to (omission of) dependency structure is negligible.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	1	0	0	0	0

- Dose-response** In the absence of other quantification methods, the concentration unit for the BSE agent is already expressed in terms of its ascribed biological effect, namely median cattle oral infectious dose (Co ID₅₀). Uncertainty arises through extrapolation from mouse ID to Co ID. The slope of the dose-response function is not considered in the estimation, which may result in an overestimation of the precision of the outcome. Therefore, a moderate level of uncertainty is attributed to the dose-response function.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
2	1	2	2	1	2	0	0	0	0

- Outcome** The final outcomes are formulated in terms of exposure with BSE infectivity (oral cattle infectious dose) of the total EU cattle population and individual cattle. We do not see uncertainty related to this outcome.

Scores:

U1	U2	U3	U4	U5	U6	K1	K2	K3	K4
1	1	1	1	1	1	0	0	0	0

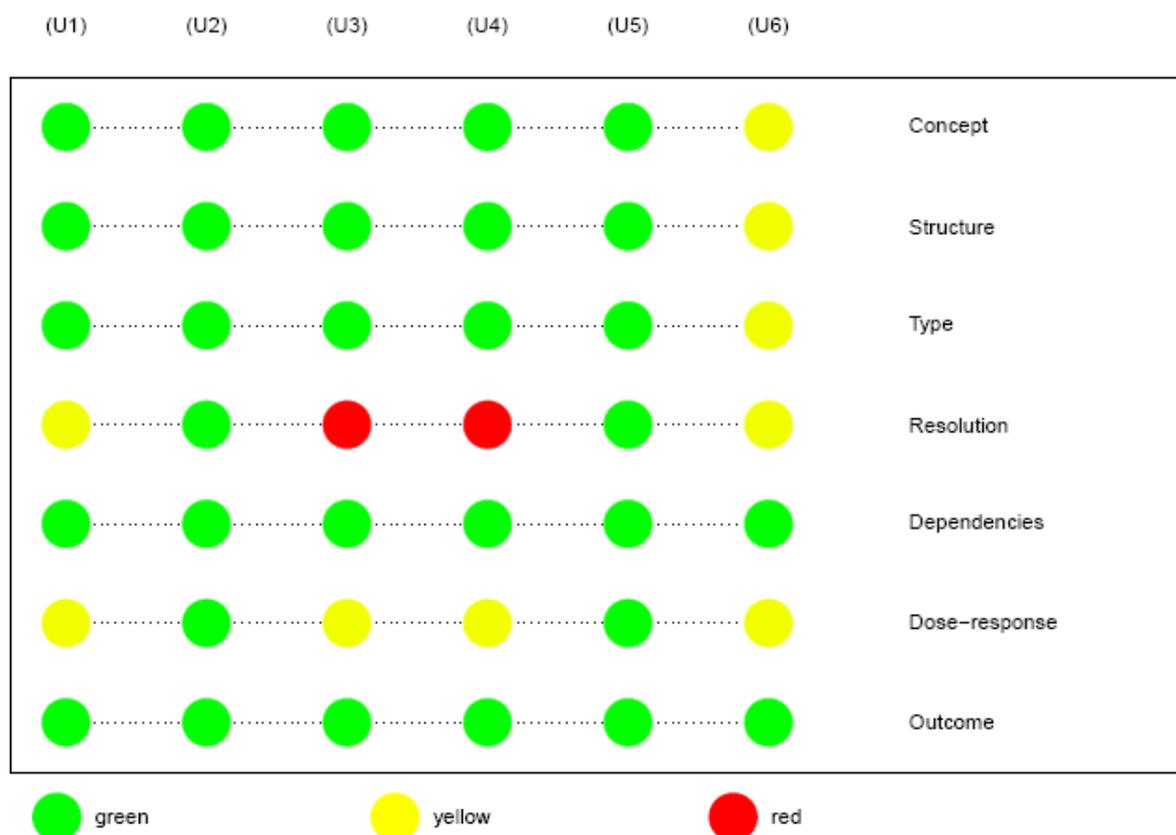


Figure 5: Scoring of modelling approach uncertainty and knowledge base: plausibility (U1), intersubjectivity (U2), choice space (U3), sensitivity to limitations (U4), sensitivity to interests (U5), influence (U6), proxy (K1), strength of evidence (K2), internal validity (K3) and external validity (K4). The qualitative scores are represented as dots using a traffic light colour scheme to signal low (green), medium (yellow) and high (red) uncertainty. No dots were drawn for criteria that were found not applicable, resulting in omission of columns for some criteria (K1, K2, K3, K4).

3. Model structure and contents

The model consists of 4 Excel worksheets, in which a total of 45 items are defined. The model has been evaluated using @RISK 4.5.5, and run using Latin Hypercube sampling with 10,000 iterations. The four sheets are summarised in the Table 9 here below.

Table 10: Summary on the information provided in the 4 sheets of the “QRA PAP model” Excel worksheet

Sheet	Description
1-Input data	<p>This sheet includes all the data used for this calculation.</p> <p>There are 3 Run Options that the user must select:</p> <p>1: Choice of BSE Prevalence Data: Default data for EU27 in 2009 is included. Or the user may specify BSE test data and related data on numbers of cattle slaughtered for any specified country or region.</p> <p>2: Rendering method: Atmospheric or Pressurised steam</p> <p>3: Batch or Continuous rendering process</p>
2-PAP to cattle	The sheet provides the calculation of exposure to individual cattle for assumed levels of contamination with PAP. Results given as Infectivity per animal per year.
3-Total exposure	This sheet provides the calculation of the total exposure to BSE infectivity for all cattle in the EU due to consumption of ruminant feed. Results given as total Infectivity per year.
4-Summary Results	This sheet copies the results from Sheet 2 and enables sets of runs (e.g. sensitivity cases) to be generated and compared easily.

Model items represent the quantitative information put into the model or derived from the model through calculation or simulation. The dependencies among model items are visualised as graph (Fig. 6).

A sensitivity analysis using tornado charts has been performed using the risk tool and is illustrated in Fig. 7. The full risk model as it was used to estimate the outcome function was compared with a relaxed model, where all distributional assumptions were replaced with uniform distributions spanning the absolute plausible ranges of each input parameter. This chart allows comparing the size and direction of the effect of all stochastic variables on the outcome of the model. Large differences of the direction and size of effects between the full and the relaxed model indicate that the outcome critically depends on the chosen distribution of uncertain parameters.

The sensitivity effects of the uncertain stochastic model inputs, along with the results of the uncertainty scoring and knowledge base are shown using a traffic light matrix in Fig. 8. Also in this case, the chart allows comparison between the full risk model as it was used to estimate the outcome function a relaxed model, where all distributional assumptions were replaced with uniform distributions spanning the absolute plausible ranges of each input parameter.

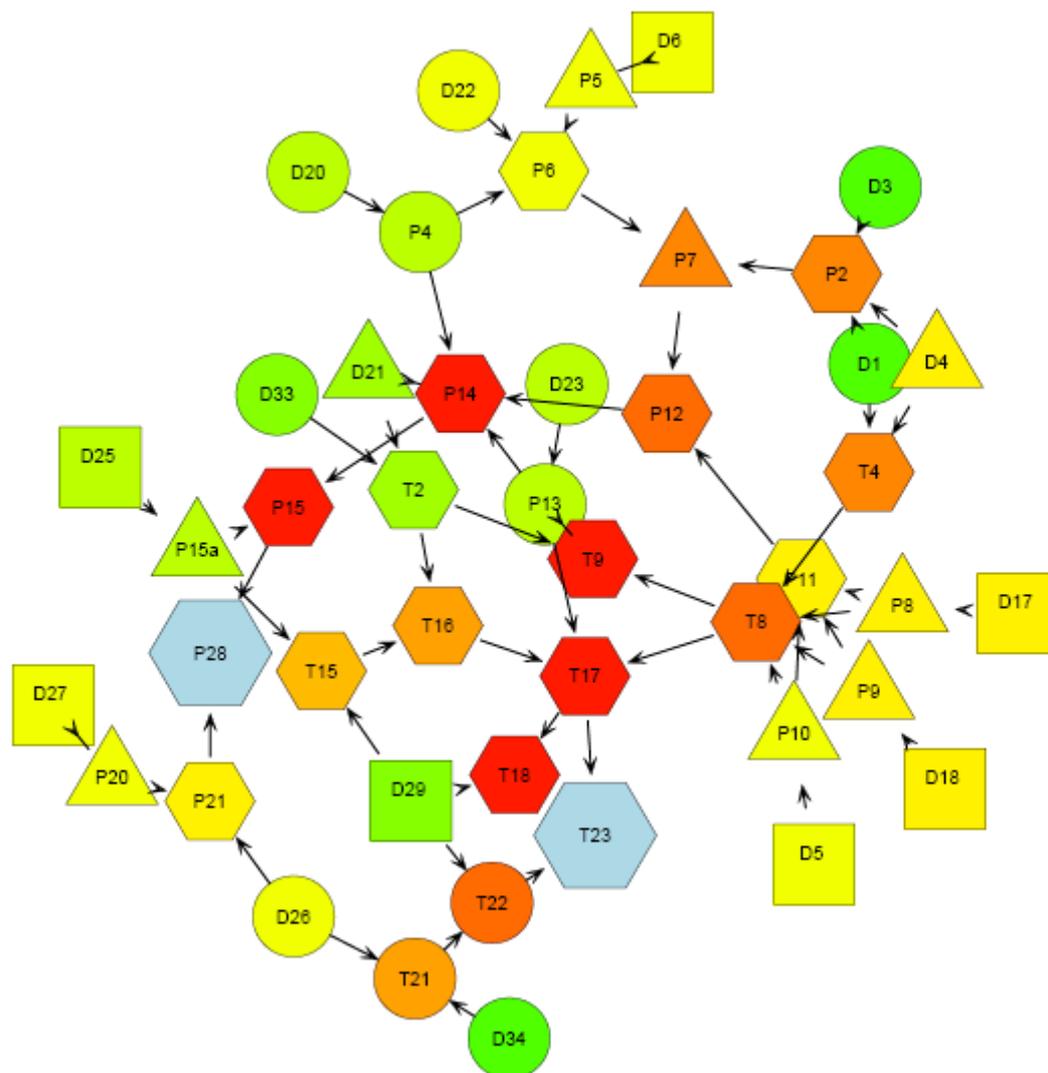


Figure 6: Dependencies among model items visualised as graph. The shape of items corresponds to the item type (square=data, triangle=mcrv, bsr, upside-down triangle=rsrv, circle=numv, pentahedron=stid-item triplet and hexahedron=fnrv-items). The colours of the items were adjusted between green and red, reflecting the lowest (most uncritical) and highest (most critical) level of uncertainty and knowledge base, respectively. The 10 qualitative scores were combined with equal weights. The item representing the outcome function (OF) is shaded in lightblue.

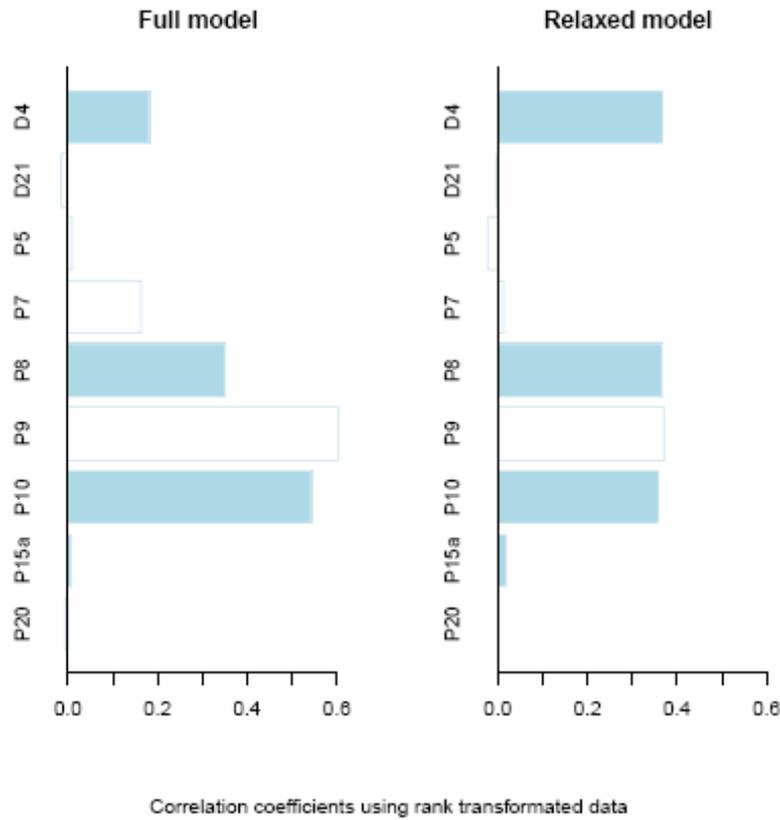


Figure 7: Tornado charts of the effect of stochastic input items on the outcome function (T23). The left figure refers to the full risk model as it was used to estimate the outcome function whereas the right figure refers to a relaxed model, where all distributional assumptions were replaced with uniform distributions spanning the absolute plausible ranges of each input parameter. Items representing variability and uncertainty are shaded in white and lightblue, respectively.

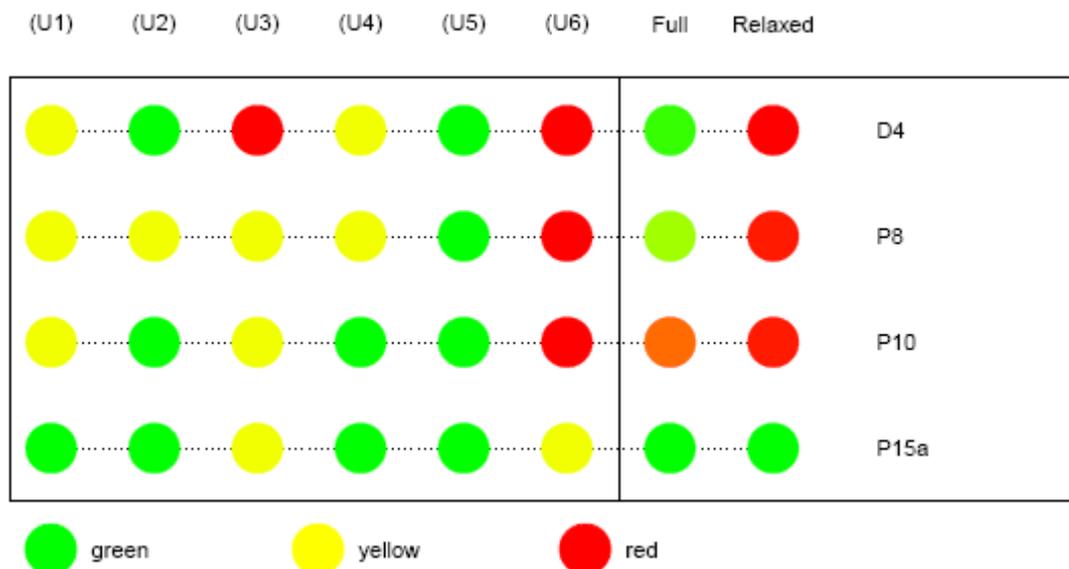


Figure 8: Uncertainty, knowledge base and effect of uncertain model items represented as dots using a traffic light colour scheme to signal non-critical (green) or critical (red) assessments and effects. Left part: qualitative assessment of plausibility (U1), intersubjectivity (U2), choice space (U3), sensitivity to limitations (U4), sensitivity to interests (U5), influence (U6), proxy (K1), strength of evidence (K2), internal validity (K3) and external validity (K4). Right part: effect on outcome function in the full and relaxed model. No dots were plotted if the qualitative assessment was 'not applicable', resulting in omission of columns for some criteria (K1, K2, K3, K4).

The descriptions of the items are grouped into three sets from the three main sheets of the EFSA QRA PAP model:

1. Input Data;
2. Parameters in the PAP to Cattle sheet;
3. Parameters in the Total Infectivity Sheet.

3.1. Input Data Sheet

3.1.1. Item D1: Number of cattle tested BSE positive

Name	D1
Explanation	Number of cattle tested BSE positive: The total number of 32 cattle (healthy slaughter, animals with clinical signs at ante mortem inspection and emergency slaughter) were tested for BSE with positive result in EU27 in 2009.
Type	Data item
Definition	32
Dependent items	P2 (Probability of BSE infection) & T4
Unit	Number of cattle
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 1 1 1
Assumptions	The cattle tested in 2009 is a good representation of cattle of various age groups entering the food and feed chain.
Remark	
References	Main report section 4.3.1, source European Commission TSE monitoring database, last accessed on 16 th November 2010.

3.1.2. Item D2: Number of cattle tested

Name	D2
Explanation	Total number of cattle tested (healthy cattle (O48M), plus animals with clinical signs at ante-mortem and emergency slaughter) in EU 27 in 2009.
Type	Data item
Definition	6,406,402
Dependent items	None
Unit	Number of cattle
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 1 1 1
Assumptions	
Remark	This number provides the total number of tested animals and so the prevalence in the tested animals. The model however uses prevalence in all slaughtered animals (D3)
References	Main report section 4.3.1, source European Commission TSE monitoring database, last accessed on 16 th November 2010.

3.1.3. Item D3: Number of cattle slaughtered

Name	D3
Explanation	Total number of cattle slaughtered in EU 27 in 2009
Type	Data item
Definition	21,018,709
Dependent items	P2 & T1
Unit	Number of cattle
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 1 1 1
Assumptions	
Remark	
References	Main report section 4.3.1, source Eurostat (http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home)

3.1.4. Item D4: Ratio undetected to detected BSE cases

Name	D4
Explanation	Ratio undetected to detected BSE cases: The number of undetected BSE infected animals per test positive animal. This estimate reflects expert opinion based on the results of multiple modelling studies (see references).
Type	Assumption with Monte Carlo distribution
Definition	Uniform distribution with range 2 to 10
Dependent items	P2 Probability of BSE infection, T4
Role	This variable represents uncertainty and variability.
Unit	Number of cattle
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 1 3 2 1 3 0 0 0 0
Assumptions	The conservative assumption was made that non-detected BSE infected animals would have a similar infectivity level as detected BSE infected animals.
Remark	This is the total number of infected animals per test positive, and does not take any account of level of infectivity. The value is pessimistic and thus may not reflect the plausible real world situation.
References	Data from a number of studies given in Main opinion section 4.3.1 (Arnold and Wilesmith, 2003; de Koeijer, 2007; Durand et al., 1999; Sala et al., 2010)

3.1.5. Item D5: BSE infectivity in bovine brain

Name	D5
Explanation	Infectivity level in brain tissue of a BSE infected bovine at clinical stage of disease. The data refer to the parameters of a log-normal distribution fitted to the 50 th and 99 th percentile values.
Type	Data item
Definition	50 th percentile (median) = 5; 99 th percentile = 100
Dependent items	P10
Unit	Co ID ₅₀ /g
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 1 2 1 1 3 0 0 0 0
Assumptions	A homogeneous distribution of infectivity in brain tissue is assumed. If this assumption is violated (i.e. if infectivity occurs in clusters), the risk outcome may show additional variability with higher risk levels occurring in rare situations. The parameters reflect a precautionary (conservative) approach.
Remark	The median value was based on published results of the VLA attack rate study (Wells et al., 2007), with the 99 th percentile set by experts and used in a number of EFSA opinions (EFSA, 2005a). This data item captures the parameters of the lognormal distribution, which are later used to define a Monte-Carlo random distribution item.
References	Main report section 4.3.7.2 (EFSA, 2005a; Wells et al., 2007)

3.1.6. Item D6: Yield of by-products

Name	D6
Explanation	Amount of by-products produced per animal at slaughter after removal of all SRMs. Data refer to mean and standard deviation of a Normal distribution. The mean value is based on information from industry while the standard deviation was assumed by experts to be one tenth of mean.
Type	Data item
Definition	Mean 167; st dev 16.7
Dependent items	P5
Unit	Kg
Scores	U1 U2U3U4U5U6K1 K2 K3 K4 2 1 2 2 1 2 0 0 0 0
Assumptions	Standard deviant assumed by experts to be one tenth of mean.
Remark	Data given as a single point value with no indication of variability, variability and uncertainty could not be differentiated.
References	Main opinion section 4.3.2, based on data from industry as reported in the EFSA QRA report (EFSA, 2005a).

3.1.7. Item D17: Probability of incomplete removal of SRM

Name	D17
Explanation	This parameter is an estimate of the likelihood that some SRM would remain in the by-products of an animal. The amount of such material is defined in Parameter D18
Type	Data item
Definition	Parameters to define a Log Normal distribution in terms of the 1 st and 99 th percentiles: 1 st percentile = 0.1%; 99 th percentile = 5%
Dependent items	P8
Unit	Fraction
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 2 2 2 1 3 0 0 0 0
Assumptions	In the QRA Report (EFSA, 2005a) it was assumed that SRM material would remain in 10% of animals slaughtered. This was reviewed by the current working group and found to be overly pessimistic. Therefore, an updated distribution was defined with a 99th percentile of 5%. The previous 10% value would be an approximate effective maximum value (99.9 percentile) in a Log Normal distribution. It is assumed that the current parameterisation is more realistic.
Remark	
References	Main opinion section 4.3.6

3.1.8. Item D18: Infected tissue per contaminated animal

Name	D18
Explanation	This item is related to the estimate of the total infected material (in terms of grams of CNS material equivalent) that may remain in the Category 3 by-products of an animal due to incomplete removal of SRM.
Type	Data item
Definition	Parameters to define a Log Normal distribution in terms of a mean value (10) with a 99 percentile value of 105
Dependent items	P9
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 2 2 2 1 3 0 0 0 0
Unit	Grams of CNS material/animal
Assumptions	This distribution has been defined by the experts of the working group following a review of the values used in the QRA Report (EFSA, 2005a), which were regarded as being highly pessimistic given the implementation of SRM controls in the EU. The 99 percentile value (105g) was set from the expected value defined in the QRA Report with a mean value a factor of 10 less.
Remark	
References	Main opinion section 4.3.6

3.1.9. Item D19: Batch size

Name	D19
Explanation	Batch size for tallow production. The total size of a batch, in terms of the amount of raw animal by-products, used to produce tallow and PAP (or MBM).
Type	Data item
Definition	150 to 1000 modelled as a Uniform distribution
Dependent items	P4
Unit	tonnes
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 2 1 1 2 0 0 0 0
Assumptions	It is assumed this range represents the possible variability of the different batch processing methods.
Remark	The user can select either Batch or Continuous rendering process in the Model set up. Prior to 2005 there were many batch processing rendering plants; most of the industry now has moved to continuous process operation. This item was not implemented in the comparative risk implementation.
References	Data on the batch sizes for rendering process were provided by industry representatives to the EU Working Group for the QRA Report (EFSA, 2005a).

3.1.10. Item D20: Batch size equivalent to model a continuous process

Name	D20
Explanation	Equivalent batch size used to model a continuous process
Type	Data item
Definition	1,000,000
Dependent items	P4
Unit	Tonnes
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 2 1 1 2 0 0 0 0
Assumptions	The current parameter is thought to reflect current production procedures. The value was selected following a set of trial runs to determine when steady state results were achieved.
Remark	The user can select either Batch or Continuous rendering process in the Model set up.
References	Main report section 4.3.4.

3.1.11. Item D21: Yield of PAP from processed by-products

Name	D21
Explanation	Yield of PAP. This is the yield of PAP per amount of raw animal by-products processed. The range between 30 and 35% reflects variability and is based on expert opinion and data.
Type	Monte Carlo random variable
Definition	Uniform distribution with range 30 to 35%
Dependent items	P14, T2
Unit	Fraction
Role	This variable represents variability only.
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 2 2 2
Assumptions	
Remark	
References	Main report section section 4.3.5, based on updated information received from the European Fat Processors and Renderers Association on 4 th May 2010.

3.1.12. Item D22: Proportion of ruminant PAP produced from bovine material

Name	D22
Explanation	Proportion of ruminant PAP produced from bovine material. The most likely value was given by experts.
Type	Data item
Definition	Value = 90%
Dependent items	P6
Unit	Fraction
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 1 2 2 1 2 0 0 0 0
Assumptions	The value was derived from the total weight of the ruminant carcasses produced each year in the EU by species and assuming that the proportion of the weight of a carcass over the total live weight of an animal is the same for bovines, sheep and goats.
Remark	
References	Main report section 4.3.3, data source Eurostat, dataset "food_in_pagr2" Slaughtered animals for food production available at the following link: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/ .

3.1.13. Items D23 and D24: BSE infectivity reduction by processing

Name	D23 and D24
Explanation	Infectivity reduction by processing. This is the expected reduction in the infectivity load in the raw material (measured in Co ID ₅₀ units) as a result of the rendering process to produce PAP. The user has the option of selecting between Atmospheric processing (base case) and Pressurised steam processing.
Type	Data item
Definition	D23: Pressurised steam processing. Values to define the minimum, best estimate and maximum values for a Triangular distribution. 10; 200; 1000 D24: Atmospheric processing. Simple value of 1
Dependent items	P13
Unit	Factor
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 2 1 1 2 0 0 0 0
Assumptions	For the base case it is assumed that most Category 3 material is now processed at atmospheric pressure and it is assumed that this would have no impact on the infectivity in the raw material. For the sensitivity case it is assumed that pressurised steam processing uses Method 1 as per Rec (EC) 1774/2002 1774/2002.
Remark	The user has the option of selecting between Atmospheric processing (base case) and Pressurised steam processing.
References	Main opinion section 4.3.10. References (Schreuder et al., 1998; Taylor et al., 1995)

3.1.14. Item D25: Proportion of contamination of non-ruminant PAP with ruminant PAP

Name	D25
Explanation	Proportion of contamination of non-ruminant PAP with ruminant PAP: The data refer to the minimum and maximum of a uniform distribution given by experts.
Type	Data item
Definition	Parameters to define the minimum and maximum values in a Uniform distribution: Min = 0%, Max = 5%
Dependent items	P15
Unit	Fraction
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 2 1 1 2 0 0 0 0
Assumptions	It is assumed that if non-ruminant PAP was allowed to be used in some animal feed (e.g. porcine PAP in poultry feed), then EU regulations would require the complete separation of both rendering and handling facilities. This items reflects the conservative assumption that non-ruminant PAP may be contaminated with ruminant PAP despite the requirements for separation of rendering facilities and handling.
Remark	
References	Main opinion section 4.3.8

3.1.15. Item D26: Contamination of ruminant feed with non-ruminant PAP

Name	D26
Explanation	Contamination of ruminant feed with non-ruminant PAP. This is the assumed level of contamination in cattle feed concentrate by non-ruminant PAP.
Type	Data item
Definition	Three set values: 0.1%, 0.02% & 2%
Dependent items	i) 0.1% - P21 & P25; ii) 0.02% - P22 & P26 iii) 2% - P23 & P27
Unit	Fraction
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 2 2 2 3 0 0 0 0
Assumptions	The base case (0.1%) is set at the level of detection of animal proteins in animal feed. This assumption may be conservative since realistic contamination levels may also be below this threshold. The 2% and 0.02% values were set for the EFSA QRA report (EFSA, 2005a) and have been retained for consistency.
Remark	Results for the 0.02% and 2% contamination levels have been given as alternative scenarios. However it should be noted that 2% contamination of ruminant feed with animal proteins would be a very high level and is extremely unlikely to occur.
References	Main opinion section 4.3.8. Reference (EFSA, 2005a).

3.1.16. Items D27 and D28: Daily consumption of cattle feed concentrate

Name	D27 and D28
Explanation	Estimated feeding rates for animals raised for beef production. Values are given for two categories of animal husbandry Intensive and Extensive. Values are defined as the mean and standard deviation for a normal distribution.
Type	Data item
Definition	D27: Intensive system. Mean 8.0; st dev 2.0 D28: Extensive system. Mean 1.5; st dev 1.0
Dependent items	i) Intensive system P20; ii) Extensive system P24
Unit	Kg/day
Scores	U1U2U3U4U5U6K1 K2 K3 K4 1 1 3 2 1 2 0 0 0 0
Assumptions	Intensive would be representative of animals fed primarily on feed concentrate. This scenario reflects the highest level of risk. Extensive system assumes some level of concentrate feeding, whilst in a truly extensive system cattle would be fed entirely on grass or conserved grass (e.g., hay/silage).
Remark	Values accepted as representative of EU by working group for the original QRA report (EFSA, 2005)
References	Main opinion section 4.3.11. Reference (EFSA, 2005a).

3.1.17. Items D29, D30, D31 and D32: Total PAP produced in EU

Name	D29, D30, D31 & D32
Explanation	Total production of PAP in EU in 2009 for Poultry (D29), Feather meal (D30), Porcine meal (D31) and all other Cat 3 PAP including ruminant (D32).
Type	Data item
Definition	D29: 372,000 D30: 215,000 D31: 375,000 D32: 1,245,000
Dependent items	T10, T11 and T12
Unit	tonnes
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 2 1 2
Assumptions	
Remark	
References	Main opinion section 4.3.9. Data for 2009 provided by European Feed Processors and Rendering Association (EFPPRA) on 20 th October 2010. The data are for the 19 EU member states that are members of EFPPRA and only exclude member states with a relatively low production.

3.1.18. Item D33: Total cat 3 ruminant material processed

Name	D33
Explanation	Total amount of ruminant category 3 material processed in the EU in 2009.
Type	Data Item
Definition	3,439,600
Dependent items	T2
Unit	tonnes/year
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 2 1 2
Assumptions	
Remark	The data are for the 19 EU member states that are members of EFPR and only exclude member states with a relatively low production.
References	Main opinion section 4.3.9. Data for 2009 provided by European Feed Processors and Rendering Association (EFPR) (Stephen Woodgate, personal communication received on 1 st December 2010).

3.1.19. Item D34: Total ruminant feed produced in EU

Name	D34
Explanation	Total ruminant feed produced in the EU27 in 2009.
Type	Data item
Definition	38,570,000
Dependent items	T19
Unit	tonnes/year
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 1 1 1 1
Assumptions	
Remark	Data for 2009
References	Main report section 4.3.9. Reference to http://www.fefac.org/

3.2. PAP to Cattle Sheet

3.2.1. Item P1: Prevalence Data Used

Name	P1
Explanation	Prevalence Data Used
Type	Input option
Definition	Default
Dependent items	P2
Unit	
Assumptions	
Remark	The user can select either the Default Data set (EU27 in 2009), or can provide specified data for individual countries on the Input Data sheet. This choice is shown here with the Data set name.
References	

3.2.2. Items P2 and P3: BSE prevalence in slaughter cattle

Name	P2 & P3																				
Explanation	BSE prevalence in slaughter cattle: Probability of BSE infection in cattle slaughtered in the EU for consumption.																				
Type	Function item using random variables																				
Definition	$D1 * D4 / D3$																				
Dependent items	P7																				
Unit	Probability																				
Scores	<table style="margin-left: auto; margin-right: auto; border: none;"> <tr> <td>U1</td><td>U2</td><td>U3</td><td>U4</td><td>U5</td><td>U6</td><td>K1</td><td>K2</td><td>K3</td><td>K4</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>2</td><td>1</td><td>3</td><td>1</td><td>1</td><td>1</td><td>1</td> </tr> </table>	U1	U2	U3	U4	U5	U6	K1	K2	K3	K4	1	2	3	2	1	3	1	1	1	1
U1	U2	U3	U4	U5	U6	K1	K2	K3	K4												
1	2	3	2	1	3	1	1	1	1												
Assumptions	It is assumed that testing of cattle over 48 months of age is continued and that BSE positive detected cases would not enter the feed chain. The probability of infection is calculated based on the results from the BSE testing programme in the EU. The data (D1) give the number of test positives in healthy slaughter cattle, those with clinical signs at ante-mortem inspection that emergency slaughter animals. These test positives would be removed from the food supply, but a number of infected but not detected animals is assumed (D4) per test positives.																				
Remark	P3 is the same parameter expressed as infections per million cattle																				
References																					

3.2.3. Item P4: Selected Batch size

Name	P4
Explanation	Selected batch size. Selected value from input data depending on whether Continuous or Batch processing is selected in the Input Options.
Type	Selected Data item
Definition	Continuous processing = D20 Batch processing = D19
Dependent items	P6, P14
Unit	tonnes
Assumptions	
Remark	
References	

3.2.4. Item P5: Yield of By-Products per animal

Name	P5
Explanation	Yield of by-products per cattle after removal of SRM. Variability modelled as Normal distribution.
Type	Monte Carlo random variate item
Definition	Normal distribution with mean and standard deviation specified as D6
Dependent items	P6
Unit	Kg/animal
Role	This variable represents variability only.
Assumptions	
Remark	
References	

3.2.5. Item P6: Number of cattle contributing to one batch

Name	P6																				
Explanation	Number of bovine animals contributing to one batch. This is the expected number of bovines that would be included in the specified batch of material. This quantity is established using the batch size in tonnes (P4), the most likely value of the fraction of bovine origin (D22) and the yield of by-product per animal (P5).																				
Type	Function item																				
Definition	$P4 * 1000 * D22 / P5$																				
Dependent items	P7																				
Unit	Number of cattle/batch																				
Scores	<table style="margin-left: auto; margin-right: auto;"> <tr> <td>U1</td><td>U2</td><td>U3</td><td>U4</td><td>U5</td><td>U6</td><td>K1</td><td>K2</td><td>K3</td><td>K4</td> </tr> <tr> <td>1</td><td>1</td><td>2</td><td>2</td><td>2</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td> </tr> </table>	U1	U2	U3	U4	U5	U6	K1	K2	K3	K4	1	1	2	2	2	3	0	0	0	0
U1	U2	U3	U4	U5	U6	K1	K2	K3	K4												
1	1	2	2	2	3	0	0	0	0												
Assumptions																					
Remark																					
References																					

3.2.6. Item P7: Number of BSE infected cattle per batch

Name	P7																				
Explanation	Number of infected animals in the batch. This is the number of infected but non-detected cattle in the batch of material, represented as a Poisson distribution																				
Type	Monte Carlo random variate item																				
Definition	Poisson ($P6 * P2$)																				
Dependent items	P12																				
Unit	Number of cattle/batch																				
Scores	<table style="margin-left: auto; margin-right: auto;"> <tr> <td>U1</td><td>U2</td><td>U3</td><td>U4</td><td>U5</td><td>U6</td><td>K1</td><td>K2</td><td>K3</td><td>K4</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>2</td><td>1</td><td>3</td><td>1</td><td>1</td><td>1</td><td>1</td> </tr> </table>	U1	U2	U3	U4	U5	U6	K1	K2	K3	K4	1	2	3	2	1	3	1	1	1	1
U1	U2	U3	U4	U5	U6	K1	K2	K3	K4												
1	2	3	2	1	3	1	1	1	1												
Assumptions	Homogeneous mixing of BSE infectivity is assumed.																				
Remark																					
References																					

3.2.7. Item P8: Probability of SRM incomplete removal

Name	P8
Explanation	Probability of SRM incomplete removal. This is the probability that some SRM material would not be removed and left in the by-products. Sampled values from a specified Log Normal distribution.
Type	Monte Carlo random variate item
Definition	As defined for D17
Dependent items	P11, T6, T8
Unit	Fraction
Role	This variable represents both uncertainty and variability.
Assumptions	
Remark	
References	

3.2.8. Item P9: Quantity of remaining SRM tissues per animal

Name	P9
Explanation	Quantity of remaining SRM tissue per animal. The distribution is thought to represent the actual situation (variability). The values are sampled from the distribution defined by item D18.
Type	Monte Carlo random variate item
Definition	As defined for D18
Dependent items	P11, T5, T8
Unit	Grams of CNS equivalent tissue/animal
Assumptions	
Remark	
References	

3.2.9. Item P10: Sampled BSE infectivity in bovine brain

Name	P10
Explanation	Sampled BSE infectivity in bovine brain. Sampled value from a specified distribution defined by item D5.
Type	Monte Carlo random variate item
Definition	As defined for D5
Dependent items	P11, T7, T8
Unit	Co ID ₅₀ /g
Role	This variable represents both uncertainty and variability.
Assumptions	
Remark	
References	

3.2.10. Item P11: Infectivity per infected animal

Name	P11
Explanation	Infectivity per infected animal. This is the estimated amount of infectivity present in the raw material per infected (but not detected) animal.
Type	Function item
Definition	$P8 * P9 * P10$
Dependent items	P12
Unit	Co ID ₅₀
Scores	U1U2U3U4U5U6K1 K2 K3 K4 0 0 0 0 0 0 0 0 0 0 0
Assumptions	There is no reduction for the fact that the levels of infectivity in the infected but not detected animals are likely to much less than that in an animal with clinical disease. This is a conservative approach.
Remark	
References	

3.2.11. Item P12: Total BSE infectivity per batch of PAP

Name	P12
Explanation	Total BSE infectivity per batch of PAP: Total infectivity in one batch before processing due to contamination with SRM from BSE infected cattle.
Type	Function item using random variates
Definition	$P7 * P11$
Dependent items	P14
Unit	Co ID ₅₀
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 2 3 2 1 3 1 1 1 1
Assumptions	
Remark	
References	

3.2.12. Item P13: BSE infectivity reduction during processing

Name	P13
Explanation	BSE infectivity reduction during processing. User selects either Atmospheric processing (Base case value) or Pressurised steam in Input Data sheet
Type	Selected data item
Definition	IF Atmospheric = D24 IF Pressurised steam = D23
Dependent items	P14, T9, T17
Unit	Factor
Assumptions	
Remark	
References	

3.2.13. Item P14: BSE infectivity in ruminant PAP

Name	P14
Explanation	BSE infectivity in ruminant PAP: This is concentration of infectivity in batch, reduced by the rendering reduction factor, divided by the total amount of PAP produced and factored by proportion from bovine source.
Type	Function item using random variates
Definition	$(P12 / P13) / (P4 * D21 * 1,000,000)$
Dependent items	P15
Unit	Co ID ₅₀ /g
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 2 3 2 2 3 1 3 3 3
Assumptions	Assumes homogenous mixing of infectivity through the batch.
Remark	
References	

3.2.14. Item P15a: Proportion of contamination of non-ruminant PAP with ruminant PAP

Name	P15
Explanation	Proportion of contamination of non-ruminant PAP with ruminant PAP: Sampled value from uniform distribution with ranges defined by D25.
Type	Monte Carlo random variable
Definition	$U(D25[1], D25[2])$
Dependent items	P15, T15
Unit	fraction
Scores	See D25
Assumptions	See D25
Remark	This item was needed in the set-up of the model in risk in order to produce the figures 4 to 8 provided in this Appendix because in risk an item cannot be used to define a distribution and a function of the distribution at the same time. Item 15a is not defined in the EFSA QRA PAP model implemented with @RISK but is directly integrated in item P15.
References	

3.2.15. Item P15: BSE infectivity of non-ruminant PAP

Name	P15
Explanation	BSE infectivity in non-ruminant PAP. Infectivity in non-ruminant PAP assuming that this is contaminated with ruminant PAP at a level of between zero and 5% (see D25).
Type	Function item using random variates
Definition	$P14 * \text{Uniform}(D25(1), D25(2))$
Dependent items	P28 (Base case), P31 & P34
Unit	Co ID ₅₀ /g
Scores	U1U2U3U4U5U6K1 K2 K3 K4 2 2 3 2 2 3 1 3 3 3
Assumptions	
Remark	
References	

3.2.16. Item P20: Sampled daily consumption of cattle feed concentrate

Name	P20
Explanation	Sampled daily consumption of cattle feed concentrate. Estimated consumption of cattle feed concentrate by beef animals in an intensive rearing system. Sampled value from a truncated Normal distribution; parameters defined in D27.
Type	Monte Carlo random variate item
Definition	Normal distribution with mean and standard deviation as defined in D27
Dependent items	P21 (Base case) and P22 & P23
Unit	Kg/day
Role	This variable represents variability only.
Assumptions	
Remark	Alternate case for less intensive feeding given by P24
References	

3.2.17. Items P21, P22 and P23: Non-ruminant PAP in cattle feed

Name	P21, P22 and P23																				
Explanation	Non-ruminant PAP in cattle feed. The estimated annual intake per animal of non-ruminant PAP in cattle feed at the selected contamination level. The base case contamination is 0.1% (P21), with alternate values being given in P22 and P23																				
Type	Function item																				
Definition	$P20 * D26 * 365 * 1000$																				
Dependent items	i) P28 for P21, ii) P31 for P22 and iii) P34 for P23																				
Unit	g/animal year																				
Scores	<table style="margin-left: auto; margin-right: auto;"> <tr> <td>U1</td><td>U2</td><td>U3</td><td>U4</td><td>U5</td><td>U6</td><td>K1</td><td>K2</td><td>K3</td><td>K4</td> </tr> <tr> <td>1</td><td>1</td><td>3</td><td>2</td><td>2</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td> </tr> </table>	U1	U2	U3	U4	U5	U6	K1	K2	K3	K4	1	1	3	2	2	3	0	0	0	0
U1	U2	U3	U4	U5	U6	K1	K2	K3	K4												
1	1	3	2	2	3	0	0	0	0												
Assumptions																					
Remark																					
References																					

3.2.18. Items P28, P31 and P34: Exposure to infectivity

Name	P28, P31 and P34																				
Explanation	The exposure to infectivity for one bovine being reared for beef in an intensive rearing system estimated as BSE infectivity in PAP per gram (P15) times the annual PAP intake in grams for an individual cattle (P21). The base case contamination is 0.1% (P28), with alternate values being given in P31 and P34.																				
Type	Function item																				
Definition	$P21 * P15$																				
Dependent items	Model Output																				
Unit	Co ID ₅₀ /animal/yr																				
Role	This item has been defined as outcome function (OF)																				
Scores	<table style="margin-left: auto; margin-right: auto;"> <tr> <td>U1</td><td>U2</td><td>U3</td><td>U4</td><td>U5</td><td>U6</td><td>K1</td><td>K2</td><td>K3</td><td>K4</td> </tr> <tr> <td>2</td><td>2</td><td>3</td><td>2</td><td>2</td><td>3</td><td>1</td><td>3</td><td>3</td><td>3</td> </tr> </table>	U1	U2	U3	U4	U5	U6	K1	K2	K3	K4	2	2	3	2	2	3	1	3	3	3
U1	U2	U3	U4	U5	U6	K1	K2	K3	K4												
2	2	3	2	2	3	1	3	3	3												
Assumptions																					
Remark	Results for alternate contamination levels give in P31 and P34, and for extensive feed system in P37, P40 & P43). Output statistics in terms of mean, and percentile values are given in P29 and P30																				
References																					

3.3. Sheet 3: Total Exposure

3.3.1. T1: Total cat 3 ruminant material processed

Name	T1
Explanation	Total amount of ruminant category 3 material processed in the EU in 2009.
Type	Selected data item
Definition	D33
Dependent items	T2
Unit	Tonnes/year
Assumptions	
Remark	
References	

3.3.2. Item T2: PAP produced from ruminant Category 3 ABP

Name	T2
Explanation	PAP produced from ruminant Category 3 ABP
Type	Function item using random variates
Definition	=T1 * D21
Dependent items	T9 & T16
Unit	Tonnes/year
Assumptions	
Remark	
References	

3.3.3. Item T3: Number of BSE positive cases

Name	T3
Explanation	No of BSE positive cases
Type	Selected data item
Definition	D1
Dependent items	T4
Unit	Number of cattle
Assumptions	
Remark	
References	

3.3.4. Item T4: Number of undetected infected cattle

Name	T4
Explanation	Number of undetected infected cattle
Type	Function item using random variates
Definition	T3 * D4
Dependent items	T8
Unit	Number of cattle
Assumptions	
Remark	
References	

3.3.5. Item T5: Quantity of remaining SRM tissues per animal

Name	T5
Explanation	Quantity of remaining SRM tissue per animal.
Type	Monte Carlo random variate item
Definition	P9
Dependent items	T8
Unit	Grams of CNS equivalent tissue/animal
Assumptions	
Remark	
References	

3.3.6. Item T6: Probability of SRM incomplete removal

Name	T6
Explanation	Probability of SRM incomplete removal. This is the probability that some SRM material would not be removed and left in the by-products. Sampled values from a specified Log Normal distribution.
Type	Monte Carlo random variate item
Definition	P8
Dependent items	T8
Unit	fraction
Assumptions	
Remark	
References	

3.3.7. Item T7: Sampled BSE infectivity in bovine brain

Name	T7
Explanation	Sampled BSE infectivity in bovine brain. Sampled value from a specified distribution.
Type	Monte Carlo random variate item
Definition	P10
Dependent items	T8
Unit	Co ID ₅₀ /g
Assumptions	
Remark	
References	

3.3.8. Item T8: Total infectivity in Cat 3 ABP

Name	T8
Explanation	Total infectivity in Cat 3 ABP. Infectivity in all ruminant category 3 ABP in the EU in one year prior to processing
Type	Function item using random variates
Definition	$T4 * T5 * T6 * T7$
Dependent items	T9, T17
Unit	Co ID ₅₀ / year
Assumptions	
Remark	
References	

3.3.9. Item T9: Concentration in ruminant PAP

Name	T9
Explanation	Concentration in ruminant PAP
Type	Function item using random variates
Definition	$T8/(P13 * T2 * 1000)$
Dependent items	T25
Unit	Co ID ₅₀ /kg
Assumptions	
Remark	
References	

3.3.10. Items T10, T11 and T12: Non-ruminant PAP produced in EU in 2009

Name	T10, T11 & T12
Explanation	Non-ruminant PAP produced in EU in 2009
Type	Data items
Definition	D29, D30 & D31
Dependent items	T13
Unit	tonnes
Assumptions	
Remark	
References	

3.3.11. Item T13: Total non-ruminant PAP produced in EU in 2009

Name	T13
Explanation	Total non-ruminant PAP produced in EU in 2009
Type	Function item
Definition	Sum of (T10, T11 & T13)
Dependent items	T15
Unit	tonnes
Assumptions	
Remark	
References	

3.3.12. Item T14: Proportion of contamination of non-ruminant PAP with ruminant PAP

Name	T14
Explanation	Proportion of contamination of non-ruminant PAP with ruminant PAP.
Type	Monte Carlo random variate item
Definition	Uniform distribution with Minimum and maximum values as per D25
Dependent items	T15
Unit	Fraction
Assumptions	
Remark	
References	

3.3.13. Item T15: Amount of ruminant PAP present in non-ruminant PAP

Name	T15
Explanation	Amount of ruminant PAP present in non-ruminant. The amount of ruminant PAP that would be present if all the non-ruminant PAP produced was contaminated at the level specified in T14
Type	Function item using random variates
Definition	$T13 * T14$
Dependent items	T16
Unit	tonnes
Assumptions	It is assumed that all the non-ruminant PAPs produced are contaminated at the level specified in T14.
Remark	
References	

3.3.14. Item T16: Proportion of total ruminant PAP

Name	T16
Explanation	Proportion of total ruminant PAP. This is the proportion of the total ruminant PAP produced represented by T15
Type	Function item using random variates
Definition	$T15 / T2$
Dependent items	T17
Unit	Fraction
Assumptions	
Remark	
References	

3.3.15. Item T17: Total infectivity in non-ruminant PAP

Name	T17
Explanation	Total infectivity in non-ruminant PAP. Infectivity in non-ruminant PAP due to contamination with ruminant PAP.
Type	Function item using random variates
Definition	$T8 * T16 / P13$
Dependent items	T18 & T23
Unit	Co ID ₅₀ / year
Assumptions	
Remark	
References	

3.3.16. Item T18: Concentration in non-ruminant PAP

Name	T18
Explanation	Concentration in non-ruminant PAP
Type	Function item using random variates
Definition	$T17 / (T13 * 1000)$
Dependent items	
Unit	Co ID ₅₀ /kg
Assumptions	
Remark	
References	

3.3.17. Item T19: Total ruminant feed produced in EU

Name	T19
Explanation	Total ruminant feed produced in the EU27 in 2009.
Type	Data item
Definition	D34
Dependent items	T21
Unit	tonnes
Assumptions	
Remark	
References	

3.3.18. Item T20: Contamination of ruminant feed with non-ruminant PAP

Name	T20
Explanation	Contamination of ruminant feed with non-ruminant PAP. This is the assumed level of contamination in cattle feed concentrate by non-ruminant PAP.
Type	Data item
Definition	D26
Dependent items	T21
Unit	Fraction
Assumptions	
Remark	
References	

3.3.19. Item T21: Total non-ruminant PAP present in cattle feed

Name	T21
Explanation	Total non-ruminant PAP present in cattle feed, if all feed produced was contaminated at the specified level. Calculated for the three specified contamination levels.
Type	Function item
Definition	$T19 * T20 = D26 * D34$
Dependent items	T22
Unit	Tonnes / year
Assumptions	
Remark	
References	

3.3.20. Item T22: Proportion of total non-ruminant PAP

Name	T22
Explanation	Proportion of total non-ruminant PAP
Type	Function item
Definition	$T21 / T13$
Dependent items	T23
Unit	Fraction
Assumptions	
Remark	Note that 2% contamination would imply that 80% of the non-ruminant PAP produced would be present in the cattle feed. This is an unrealistic assumption
References	

3.3.21. Item T23: Total infectivity in ruminant feed

Name	T23
Explanation	Total infectivity in ruminant feed. Estimated total infectivity in all ruminant feed produced in the EU for specified contamination levels.
Type	Function item using random variates
Definition	$T17 * T22$
Dependent items	T24
Role	This item has been defined as outcome function (OF)
Unit	Co ID ₅₀ / year
Assumptions	This assumes that all the ruminant feed produced in the EU is contaminated at the same level.
Remark	
References	

3.3.22. Item T24: Calculation of R₀ values

Name	T24
Explanation	R ₀ . Calculated R ₀ value for given contamination level. R ₀ represents the expected number of new infections per infected animal entering the system
Type	Function item using random variates
Definition	$(T23 * 0.5) / T4$
Dependent items	Model Output
Unit	Fraction
Assumptions	
Remark	
References	

GLOSSARY

Term	Definition
Animal By-Products (ABPs)	Entire bodies or parts of animals or products of animal origin referred to in Articles 4, 5 and 6 of the Reg. (EC) 1774/2002 not intended for human consumption, including ova, embryos and semen.
Atypical Bovine Spongiform Encephalopathy (Atypical BSE)	Two distinct types of cattle TSEs, termed H- and L-type Atypical BSE, which are commonly known as Atypical BSE.
BASE	A synonymous for L-type Atypical BSE; see Atypical Bovine Spongiform Encephalopathy.
Basic reproduction ratio (R_0)	The number of secondary cases caused by the introduction of 1 infected animal.
Born After the Re-inforced Ban (BARB)	The BSE cases resulting in cattle born after UK re-inforced feed ban.
Category 3 Animal By-Products	The Animal By-Products described under Article 6, point 1 of Reg. (EC) 1774/2002.
Cattle oral Infectious Dose 50% ($Co ID_{50}$)	The oral dose which infects 50% of cattle in an experimental test.
Central Nervous System (CNS)	The portion of the vertebrate nervous system consisting of the brain and spinal cord (Biology on line: www.biology-online.org).
Classical Bovine Spongiform Encephalopathy (Classical BSE)	A transmissible spongiform encephalopathy (see below) of adult cattle. Contamination of MBM in feed with prions is considered to have caused the BSE epidemic that originated in the late 1980s in the UK.
DRG	Dorsal Root Ganglia
Geographical Risk of Bovine Spongiform Encephalopathy (GBR)	The Geographical BSE-Risk (GBR) is a qualitative indicator of the likelihood of the presence of one or more cattle being infected with BSE (Bovine Spongiform Encephalopathy), pre-clinically as well as clinically, at a given point in time, in a country. According to the Scientific Steering Committee (SSC) Opinion on the geographical BSE-risk (GBR) and its evolution over time in the European Union Member States, adopted on 21/22 February 2002 (http://europa.eu.int/comm/food/fs/sc/ssc/out249_en.pdf) four GBR categories were defined: i) GBR I: Highly unlikely; ii) GBR II: Unlikely but not excluded; iii) GBR III: Likely but not confirmed or confirmed, at a lower level; iv) GBR IV: Confirmed, at a higher level.
H-type Atypical BSE (H-BSE)	See Atypical Bovine Spongiform Encephalopathy.

Term	Definition
Intracerebral Infectious Dose 50% (Ic ID ₅₀)	The intracerebral dose which infects 50% of animals in an experimental test.
Intraperitoneal Infectious Dose 50% (Ip ID ₅₀)	The intraperitoneal dose which infects 50% of animals in an experimental test.
LOD	Limit Of Detection
L-type Atypical BSE (L-BSE or BASE)	See Atypical Bovine Spongiform Encephalopathy.
Meat and Bone Meal (MBM)	In Commission Directive 92/87/EEC of 26 October 1992 is defined as: “ <i>Product obtained by heating, drying and grinding whole or parts of warm-blooded land animals from which the fat may have been partially extracted or physically removed. The product must be substantially free of hooves, horn, bristle, hair and feathers, as well as digestive tract content. (1) Products containing more than 13 % fat in the dry matter must be named as 'rich in fat'</i> ”. It is used as a protein source in animal feed.
Meat Meal (MM)	In Commission Directive 92/87/EEC of 26 October 1992 is defined as: “ <i>Product obtained by heating, drying and grinding whole or parts of warm-blooded land animals from which the fat may have been partially extracted or physically removed. The product must be substantially free of hooves, horn, bristle, hair and feathers, as well as digestive tract content. (Minimum crude protein content 50 % on a dry matter basis)</i> ”. It is used as a protein source in animal feed.
NIRM	Near Infrared Microscopy
Prion	Neologism for “proteinaceous infectious particle”, frequently used as designation for the infectious agent of TSEs (see below). All known prions contain misfolded isomers of a normal cellular protein (PrP ^c). Aggregates of the misfolded protein of sufficient quantity and size are usually associated with TSE infectivity and neurodegenerative diseases in both animals and humans. According to the methodology used for detection of the disease associated, misfolded protein, different terms have been used for its destination (see below). Currently the preponderant hypothesis concerning prions considers that the misfolded protein is the only component of the infectious agent of TSEs. However, a part of TSE experts believe that the protein-only theory has not been proven beyond question.
Processed Animal Protein (PAP)	In Commission Regulation (EC) No 829/2007 of 28 June 2007, amending Annexes I, II, VII, VIII, X and XI to Regulation (EC) No 1774/2002 of the European Parliament and of the Council as regards the placing on the market of certain animal by-products, is defined as: “ <i>animal protein derived entirely from Category 3 material, which have been treated in accordance with Chapter II of Annex VII so as to render them suitable for direct use as feed material or for any other use in feedingstuffs, including petfood, or for use in organic fertilisers or soil improvers; however, it does not include blood products, milk, milk-based products, colostrum, gelatine, hydrolysed proteins and dicalcium phosphate, eggs and egg-products, tricalcium phosphate and collagen</i> ”. It comprises MBM and MM (see above). It is used as a protein source in animal feed.

Term	Definition
PrP ^{sc}	Term originally derived from scrapie associated PrP, but also more generally used in all TSEs. Abnormally folded prion protein that has a gradient of resistance to proteinase K digestion. It is associated with infectious potential and with prion disease even in circumstances where it may be sensitive to proteinase K digestion.
Quantitative Risk Assessment (QRA)	A risk assessment that provides numerical expressions of risk and indication of the attendant uncertainties
Specified Risk Material (SRM)	<p>According to Annex V to Reg. (EC) 999/2001 as amended:</p> <p>1. Definition of specified risk material</p> <p>The following tissues shall be designated as specified risk material if they come from animals whose origin is in a Member State or third country or of one of their region with a controlled or undetermined BSE risk:</p> <p>(a) as regards bovine animals:</p> <ul style="list-style-type: none"> (i) the skull excluding the mandible and including the brain and eyes, and the spinal cord of animals aged over 12 months; (ii) the vertebral column excluding the vertebrae of the tail, the spinous and transverse processes of the cervical, thoracic and lumbar vertebrae and the median sacral crest and wings of the sacrum, but including the dorsal root ganglia, of animals aged over 30 months; and (iii) the tonsils, the intestines from the duodenum to the rectum and the mesentery of animals of all ages. <p>(b) as regards ovine and caprine animals</p> <ul style="list-style-type: none"> (i) the skull including the brain and eyes, the tonsils and the spinal cord of animals aged over 12 months or which have a permanent incisor erupted through the gum, and (ii) the spleen and ileum of animals of all ages. <p>2. Derogation for Member States</p> <p>By way of derogation from point 1, tissues listed in that point whose origin is in Member States with a negligible BSE risk shall continue to be considered as specified risk material.</p>
Transmissible Spongiform Encephalopathy (TSE)	A family of slowly progressive and ultimately fatal diseases of the central nervous system. They are characterized by transmissibility with a long incubation period, and spongiform degeneration of the central nervous system without inflammation and immunity response. Examples in humans include CJD and kuru. Among animals: scrapie and BSE. A synonym for TSE is prion disease.