

**REPORT OF THE MEETING OF THE OIE AD HOC GROUP
ON BOVINE SPONGIFORM ENCEPHALOPATHY RISK ASSESSMENT AND SURVEILLANCE
Paris, 18-21 March 2019**

The OIE *ad hoc* Group on bovine spongiform encephalopathy (BSE) risk assessment and surveillance (hereafter the Group) met from 18 to 21 March 2019 at the OIE Headquarters to complete the revision of the BSE standards initiated by the *ad hoc* Group on BSE risk assessment which met in July and November 2018 and the *ad hoc* Group on BSE surveillance which met in October 2018.

1. Opening

Dr Matthew Stone, OIE Deputy Director General for International Standards and Science welcomed the Group on behalf of Dr Monique Eloit, Director General of the OIE. He noted that all experts had participated in one or both of the previous *ad hoc* Groups on BSE risk assessment and BSE surveillance.

Dr Stone acknowledged the significant achievements made to date in the revision of the BSE standards and emphasised that this meeting aimed to complete the revision of the provisions, including those for which the previous *ad hoc* Groups did not reach a consensus. He underlined the importance of open discussions based of scientific evidence aiming at developing risk-based provisions.

Dr Bernardo Todeschini, representative of the Terrestrial Animal Health Standards Commission (hereafter the Code Commission), emphasised that the revision of the BSE standards was considered a priority for OIE Members.

Dr Baptiste Dungu, representative of the Scientific Commission for Animal Diseases (hereafter the Scientific Commission), informed the Group that at its February 2019 meeting, the Scientific Commission emphasised the importance for the provisions for atypical BSE to be evidence-based and risk-based. He appreciated that the Group prepared a review on atypical BSE to support its discussions.

The experts were thanked for having signed the forms for undertaking of confidentiality and declaration of conflicts of interest. No potential conflict of interest in the revision of BSE Standards was declared.

2. Adoption of the agenda and appointment of chairperson and rapporteur

Dr Stephen Cobb was appointed Chair and Dr Alicia Cloete was the rapporteur with the support of the OIE Secretariat. The Group endorsed the proposed agenda for the meeting.

Dr Stone commended Dr Noel Murray for chairing the *ad hoc* Groups on BSE risk assessment and BSE surveillance.

The terms of reference, agenda and list of participants are provided as Appendices I, II and III respectively.

3. Atypical BSE

The Group discussed and endorsed with minor revisions an overview of relevant literature on the risk of atypical BSE being recycled in a cattle population and its zoonotic potential that had been prepared ahead of the meeting by one expert from the Group. This overview is provided as [Appendix IV](#) and its main conclusions are outlined below.

With regard to the risk of recycling of atypical BSE, recently published research confirmed that the L-type BSE prion (a type of atypical BSE prion) may be orally transmitted to calves¹. In light of this evidence, and the likelihood that atypical BSE could arise as a spontaneous disease in any country, albeit at a very low incidence, the Group was of the opinion that it would be reasonable to conclude that atypical BSE is potentially capable of being recycled in a cattle population if cattle were to be exposed to contaminated feed. Therefore, the recycling of atypical strains in cattle and broader ruminant populations should be avoided.

The Group acknowledged the challenges in demonstrating the zoonotic transmission of atypical strains of BSE in natural exposure scenarios. Overall, the Group was of the opinion that, at this stage, it would be premature to reach a conclusion other than that atypical BSE poses a potential zoonotic risk that may be different between atypical strains.

4. Definitions of meat-and-bone meal (MBM) and greaves

The Group discussed and endorsed a document prepared ahead of the meeting by two experts of the Group on the definitions of meat-and-bone meal (MBM) and greaves.

According to the Glossary of the *Terrestrial Animal Health Code* (hereafter the *Terrestrial Code*), MBM currently “means the solid protein products obtained when animal tissues are rendered, and includes any intermediate protein product other than peptides of a molecular weight less than 10,000 daltons and amino-acids” and greaves “means the protein-containing residue obtained after the partial separation of fat and water during the process of rendering”. The Group considered that the rationale to differentiate MBM and greaves was unclear. The Group also emphasised a lack of common understanding in different countries of what greaves are as well as a variety of practices as to how greaves are used.

The Group pointed out that, based on this definition, it was unclear whether greaves could be considered intermediate protein products. If so, it would be relevant to include greaves and MBM in a single definition.

The Group proposed a definition of “*protein meal*” encompassing both MBM and greaves as follows: “*protein meal means any final or intermediate solid protein-containing product, obtained when animal tissues are rendered, excluding blood and blood products, peptides of a molecular weight less than 10,000 daltons and amino-acids*”.

The Group noted that MBM (and greaves) were relevant not only for BSE but also for other OIE listed diseases (i.e., Chapter 8.1. on anthrax; Chapter 8.4. on infection with *Brucella abortus*, *B. melitensis* and *B. suis*; Chapter 8.11. on infection with *Mycobacterium tuberculosis* complex; Chapter 14.8. on scrapie; and Chapter 15.3 on infection with porcine reproductive and respiratory syndrome virus).

The Group recommended the proposed definition of “*protein meal*” should apply, at this stage, for the purpose of Chapters 11.4. and 1.8. of the *Terrestrial Code*. Whether this definition would also be relevant for the other disease-specific Chapters listed above should be further assessed by the OIE. If considered relevant for other diseases, the proposed definition could ultimately replace the definitions of MBM and greaves in the Glossary of the *Terrestrial Code*.

¹ Okada H, Iwamaru Y, Imamura M, Miyazawa K, Matsuura Y, Masujin K, Murayama Y, Yokoyama T. Oral transmission of L-Type bovine spongiform encephalopathy agent among cattle. *Emerging Infectious Diseases*. 2017 Feb; **23**(2):284.

5. Revision of Chapter 11.4. of the *Terrestrial Code*

5.1. Draft Article 11.4.1. General provisions

The Group revised draft Article 11.4.1. to ensure better alignment with the recommended structure of disease-specific Chapters of the *Terrestrial Code*. To improve clarity, the Group agreed to add definitions of terms applicable to this Chapter, including a case definition.

To address a question raised by the Scientific Commission at its February 2019 meeting, and consistent with the rationale of the ad hoc Group on BSE risk assessment at its November 2018 meeting, the Group concluded that the occurrence of a case of atypical BSE, regardless of the origin (imported or indigenous), would not impact a country's BSE risk status by itself (see section 5.4. of this report). Nevertheless, based on the consideration of recent findings for L-type BSE presented above and provided in Appendix IV, the Group emphasised that the potential recycling of all BSE agents, not only of classical BSE, was important to be considered in the exposure assessment. For this, atypical BSE is not completely disregarded in the recognition of a country's BSE risk status as the existing Article 11.4.1. implies. To avoid misleading statements, the phrase "*For the purposes of official BSE risk status recognition, BSE excludes 'atypical BSE' as a condition believed to occur spontaneously in all cattle populations at a very low rate*" was proposed to be removed from Article 11.4.1. The Group consequently amended draft Articles 11.4.1. and 11.4.2. point 1.b. to indicate the potential for atypical BSE to be recycled in a cattle population if cattle were to be exposed to contaminated feed, and draft Article 11.4.3. points 3.a. and 4. to clarify the impact and the way to address atypical BSE cases (section 5.4. of this report).

5.2. Draft Article 11.4.1.bis. Safe commodities

With regard to safe commodities, the Group took note of the definition provided in the Glossary of the *Terrestrial Code* (i.e., "means a commodity that can be traded without the need for risk mitigation measures specifically directed against a particular listed disease, infection or infestation and regardless of the status of the country or zone of origin for that disease, infection or infestation") as well as the provisions of the recent Chapter 2.2. of the *Terrestrial Code* (Criteria applied by the OIE for assessing the safety of commodities, first adopted in May 2017).

The Group noted that for the commodities listed under current Article 11.4.1. points 1.g. and 1.h., measures specifically directed against BSE to mitigate the risk of cross contamination by the BSE agent were explicitly stated. Point 1.g.: "deboned skeletal muscle meat (excluding mechanically separated meat) from cattle which passed ante- and post-mortem inspections; which were not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process, prior to slaughter; and which has been prepared in a manner to avoid contamination with tissues listed in Article 11.4.14."; and point 1.h.: "blood and blood by-products from cattle which were not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process, prior to slaughter"). Considering that inclusion of these commodities in an Article specifically listing safe commodities is no longer consistent with either the Glossary or Chapter 2.2., the Group sought advice from the Code Commission and agreed with their recommendation that these commodities should not be listed as safe commodities and would need to be addressed in separate articles of Chapter 11.4. (i.e., Draft Articles 11.4.9. to 11.4.11. and 11.4.13.)

The Group noted that "semen and in vivo derived cattle embryos" were listed as safe commodities in current Article 11.4.1. point 1.b. and discussed whether in vitro derived cattle embryos could also be considered safe commodities. Considering that scientific evidence was only published on in vivo derived cattle embryos² the Group could not recommend in vitro derived cattle embryos be specifically listed as safe commodities.

² Wrathall AE, Brown KF, Sayers AR, Wells GA, Simmons MM, Farrelly SS, Bellerby P, Squirrell J, Spencer YI, Wells M, Stack MJ. Studies of embryo transfer from cattle clinically affected by bovine spongiform encephalopathy (BSE). *Veterinary Record*. 2002; **150**(12):365-378.

The Group pointed out that “semen and in vivo derived cattle embryos” should not necessarily only be “collected and handled in accordance with the recommendations of the International Embryo Transfer Society” as recommended in current Article 11.4.1. point 1.b., but rather in accordance with relevant Chapters of the *Terrestrial Code*.

To address a request received by the OIE from the European Serum Products association, the Group discussed whether animal serum used in culture media could be considered a safe commodity. The Group pointed out that under current Article 11.4.1. point 1.h., the provisions for BSE pertaining to “blood and blood by-products” applied to “animal serum used in culture media”, meaning risks are effectively managed as long as this blood by-product originates from cattle which were not subjected to a stunning process with a device injecting compressed air or gas into the cranial cavity, or to a pithing process, prior to slaughter. These requirements are included in draft Article 11.4.13.

5.3. Draft Article 11.4.2. The BSE risk of the cattle population of a country, zone or compartment

The Group clarified that the BSE risk status of a cattle population should be determined based on: (i) a comprehensive risk assessment, (ii) the continuous implementation of a passive surveillance programme to detect the emergence or re-emergence of classical BSE, and (iii) the history of occurrence and management of cases of classical or atypical BSE.

The Group reviewed the listed steps of a risk assessment for the purpose of BSE. The Group complemented the provisions on the last step of the assessment (i.e., risk estimation) to better capture the expected outcome of the risk estimation (i.e., “*provide an overall measure of the risk that BSE agents have been recycled in the cattle population through the feeding of ruminant-derived protein meal, with indigenous cases arising as a consequence*”).

The Group agreed that consistent with the provisions of current Article 11.4.2., Members should review their BSE risk assessment annually.

5.4. Draft Article 11.4.3. Negligible BSE risk

The Group reviewed draft Article 11.4.3. and addressed unresolved issues from an earlier meeting of the *ad hoc* Group on BSE risk assessment, as well as the questions raised by the Scientific Commission at its February 2019 meeting.

a) *Demonstration of the implementation of a ruminant-to-ruminant feed ban*

At its November 2018 meeting, the *ad hoc* Group on BSE risk assessment did not decide whether demonstrating that protein meal derived from ruminants have not been fed to ruminants:

- could be considered to be implicitly encompassed in draft Article 11.4.3. point 1.a. as drafted in November 2018 (i.e., “*a risk assessment should demonstrate that the likelihood of cattle population being exposed to BSE agent has been negligible for at least 8 years*”); or
- should be made explicit for the sake of clarity, common understanding by Members, and therefore harmonised implementation of Article 11.4.3.

The Group agreed to complement draft Article 11.4.3. points 1.a. and 1.b. to clearly emphasise that protein meal derived from ruminants should not have been fed to ruminants regardless of the pathway for achieving a negligible BSE risk status (i.e., husbandry practices or effective and continuous mitigation of each identified risk).

b) Impact of the occurrence of case(s) of BSE

Consistent with the approach proposed in section 5.1. of this report, the Group further amended draft Article 11.4.3. point 3.a. to clearly state that the Member could be granted a negligible BSE risk status provided that if there has been a case, this case was either imported or diagnosed as atypical BSE.

At its November 2018 meeting, the *ad hoc* Group on BSE risk assessment noted that draft Article 11.4.3. needed to be further revised to clearly state that if there has been an indigenous case of classical BSE in an animal born 8 or less years ago in a country or zone already recognised as posing a negligible BSE risk, the Member could regain its negligible BSE risk status provided that a subsequent investigation confirmed that the likelihood of the BSE agent being recycled within the cattle population remained negligible. The Group accordingly amended draft Article 11.4.3. point 3.b.ii.

c) Complete destruction or disposal of any cases of BSE

At its February 2019 meeting, the Scientific Commission requested clarifications on whether the last provision of draft Article 11.4.3. (which requested that any cases of BSE have been completely destroyed) also applied to atypical BSE. In accordance with the overview on “Atypical BSE: the risk of being recycled in a cattle population and its zoonotic potential” (section 3 of this report and Appendix IV), the Group re-affirmed its previous position and, to improve clarity, amended draft Article 11.4.3. point 4., indicating that any cases of BSE either classical or atypical that have been detected should be completely destroyed or disposed of in such a way that ensures they do not enter the animal feed chain to prevent the recycling of BSE agents.

5.5. Draft Article 11.4.4. Controlled BSE risk

The Group refined draft Article 11.4.4. to ensure consistency of wording and numbering with draft Article 11.4.3.

5.6. Current Article 11.4.6. Recommendations for importation of bovine commodities from a country, zone or compartment posing a negligible BSE risk

The Group agreed with the opinion of the *ad hoc* Group on BSE which met in August 2016 which emphasised that provisions of current Article 11.4.6. were not applicable to commodities listed as safe commodities (current Article 11.4.1.) or to commodities for which recommendations were prescribed in other articles of Chapter 11.4. (i.e., current Articles 11.4.7., 11.4.10., and from 11.4.13. to 11.4.18.). The Group reviewed the list of commodities addressed in the other relevant articles of Chapter 11.4. and could not identify any remaining commodities which were not covered. The Group therefore recommended Article 11.4.6. be removed.

5.7. Draft Article 11.4.6. Recommendations for importation of cattle from a country, zone or compartment posing a negligible BSE risk

The Group noted that current Article 11.4.7. provided recommendations for the importation of cattle from a country, zone or compartment posing a negligible BSE risk but where there has been an indigenous case. The Group considered that in light of the provisions of draft Article 11.4.3., which clearly define the conditions related to the occurrence of an indigenous case, it was no longer relevant to provide such recommendations. The same recommendations would apply for the importation of live cattle from any country, zone or compartment posing a negligible BSE risk. The title of the draft article was amended accordingly.

The Group noted that current Article 11.4.7. point 1. on the permanent identification of cattle required measures to be taken on same feed cohort or birth cohort animals when an indigenous case of classical BSE was identified. Consistent with the recommendations of the *ad hoc* Group on BSE risk assessment at its July 2018 meeting, the Group agreed that the measures for cohort animals would not provide a significant gain in risk reduction as long as the likelihood of BSE being recycled within the cattle population continues to be negligible. As a result, the Group concluded that current Article 11.4.7. point 1. was no longer necessary.

Regarding the requirement of current Article 11.4.7. point 2. that cattle were born “*after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants had been effectively enforced*”, the Group advised that rather the cattle were born in the country, zone or compartment “*during the period when the likelihood of the BSE agent being recycled in the cattle population has been demonstrated to be negligible*”, consistent with Draft Article 11.4.3. point 1.

The Group discussed the provisions for trade that should apply to cattle older than the period for which the likelihood of the BSE agent being recycled in the cattle population has been assessed to be negligible. The Group noted that a country or zone applying for the official recognition of a negligible BSE risk status may be able to demonstrate that the likelihood of the BSE agent being recycled in the cattle population has been negligible for more than 8 years. In that case, this should be acknowledged in the report of the *ad hoc* Group on BSE Risk Status Evaluation of Members. This would allow countries or zones newly recognised as having a BSE negligible risk status to export cattle older than 8 years based on the provisions of draft Article 11.4.6. The Group emphasised that it should be possible for an applicant Member to document the BSE risk assessment for a period of more than eight years and that it would be necessary to make it explicit in the relevant sections of the BSE questionnaire.

5.8. Draft Article 11.4.7. Recommendations for importation of cattle from a country, zone or compartment posing a controlled BSE risk

Consistent with the approach proposed in draft Article 11.4.6., the Group advised that the provisions on the permanent identification of cattle were no longer necessary and that the cattle selected for export should be born in the country, zone or compartment during the period when the likelihood of the BSE agent being recycled in the cattle population has been demonstrated to be negligible. Consequently, this period should be acknowledged in the report of the *ad hoc* Group on BSE Risk Status Evaluation of Members.

5.9. Draft Article 11.4.8. Recommendations for importation of cattle from a country, zone or compartment posing an undetermined BSE risk

The Group reviewed the recommendations listed in current Article 11.4.9. (Recommendations for the importation of cattle from a country, zone or compartment posing an undetermined BSE risk) and pointed out that compliance with the provisions listed in points 1 (“*the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants has been banned and the ban has been effectively enforced*”) and 3.b. (cattle selected for export “*were born at least two years after the date from which the ban on the feeding of ruminants with meat-and-bone meal and greaves derived from ruminants was effectively enforced*”) would be difficult to institute and assess considering that a feed ban may not have been implemented in countries, zones or compartments posing an undetermined BSE risk.

The Group therefore recommended that draft Article 11.4.8. should focus on the demonstration that an individual animal has never been fed with feed containing ruminant-derived protein meal (see section 4 of this report). The Group acknowledged that this would be difficult to certify and that a permanent individual identification, recording and traceability system from birth and throughout the lifetime of the animal prior to export would be a pre-requisite to allow such a demonstration to be made. This option would, however, allow for bilateral negotiations of such trade.

5.10. Draft Article 11.4.9. Recommendations for importation of fresh meat and meat products from a country, zone or compartment posing a negligible BSE risk

The Group reviewed the recommendations listed in current Article 11.4.10., and, consistent with the proposed approach in draft Article 11.4.6., the Group recommended that meat and meat products imported from a country, zone or compartment posing a negligible BSE risk should be derived from cattle that passed ante-mortem inspection and were born during the period when the likelihood of the BSE agent being recycled in the cattle population has been assessed to be negligible. The Group proposed alternative provisions for meat and meat products derived from cattle that were not born during this period.

The Group reviewed the recommendation made by the *ad hoc* Group on BSE which met in August 2016 proposing that the fresh meat and meat products imported from a country, zone or compartment posing a negligible BSE risk should be produced and handled in a manner which ensures that such products do not contain and are not contaminated with skull, brain, eyes and spinal cord and mechanically separated meat from the skull from cattle over 60 or 72 months of age. Considering that, based on the provisions of draft Article 11.4.3., the likelihood of the BSE agents (atypical and classical) being recycled in the cattle population would have been demonstrated to be negligible, and acknowledging that atypical BSE would remain at a very low level and with a potential uniform presentation in any cattle population, the Group considered that specific recommendations targeting atypical BSE for international trade from a country, zone or compartment posing a negligible BSE risk would be disproportionate to the likely level of risk. As a result, the Group did not fully endorse the proposal made by the 2016 *ad hoc* Group on BSE.

The Group emphasised that *post-mortem* inspection is not considered relevant for BSE and recommended any reference to *post-mortem* inspection to be removed throughout draft Chapter 11.4.

5.11. Draft Article 11.4.10. Recommendations for importation of fresh meat and meat products from a country, zone or compartment posing a controlled BSE risk

The Group reviewed the recommendations listed in current Article 11.4.11. and only made editorial changes for the sake of clarity and harmonisation with draft Article 11.4.11.

5.12. Draft Article 11.4.11. Recommendations for importation of fresh meat and meat products from a country, zone or compartment posing an undetermined BSE risk

The Group reviewed the recommendations listed in current Article 11.4.12. and agreed with the opinion of the *ad hoc* Group on BSE which met in August 2016 that point 2.b. of current Article 11.4.12., should be removed. Point 2.b. currently recommends that fresh meat and meat products should be produced and handled to ensure that such products do not contain and are not contaminated with nervous and lymphatic tissues exposed during the deboning process. The Group agreed that these measures would have been implemented out of an abundance of caution based on a comparison with scrapie. Indeed, pathogenesis studies have subsequently confirmed that BSE in cattle amplifies almost exclusively in the CNS and the ileal Peyer's patches, with later limited centrifugal spread of infectivity along nerve fibres into the periphery in the clinical stages of the disease^{3, 4}. As a result, the Group concluded that the removal of these tissues is not relevant to mitigate the BSE risk.

The Group noted that current Article 11.4.12. point 2.c. required that fresh meat and meat products should be produced and handled in a manner which ensures that such products do not contain and are not contaminated with mechanically separated meat from the skull and from the vertebral column from cattle over 12 months of age. The Group discussed the age limit of 12 months and agreed that it was originally implemented out of an abundance of caution in the early 2000s when there was significant uncertainty. However, experiences gained since then have confirmed that the occurrence of clinical cases in cattle less than three years of age is a rare event. For example, even in Great Britain, the country with the highest levels of exposure to BSE, only 0.15% of almost 137,000 BSE cases, for which there was reliable age data, were less than 36 months of age over the course of the entire epidemic⁵. In addition, experimental oral challenge studies in cattle with a one-gram dose of highly infectious brain material indicate that the detection of infectivity in central nervous system (CNS) in the majority of animals likely occurs only after 42 months-post-exposure (Arnold *et al.*, 2007). The one-gram dose used in this study is likely to represent a reasonable worst-case exposure scenario for naturally infected cattle. Considering that the average

³ Espinosa JC, Morales M, Castilla J, Rogers M, Torres JM. Progression of prion infectivity in asymptomatic cattle after oral bovine spongiform encephalopathy challenge. *Journal of General Virology*. 2007; **88**, 1379-1383.

⁴ Balkema-Buschmann A, Fast C, Kaatz M, Eiden M, Ziegler U, McIntyre L, Keller M, Hills B, Groschup MH. Pathogenesis of classical and atypical BSE in cattle. *Preventive Veterinary Medicine*. 2011; **102** (2):112-117.

⁵ Animal and Plant Health Agency (March 2019). (1) Age related statistics, available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/795724/pub-tse-stat-age.pdf, and (2) General statistics on BSE cases in Great Britain, available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/795723/pub-tse-stat-gen.pdf

incubation period of cattle infected in the field is in the range of 5.0 to 5.5 years, these authors considered that their findings “offer considerable scope for modulation of current regulations”. The Group concluded that maintaining an age limit of 12 months would be disproportionate to the level of risk and recommended it be aligned with the age limit suggested for the importation of meat and meat products from a country, zone or compartment posing a controlled BSE risk (i.e., 30 months).

5.13. Draft Article 11.4.12. Recommendations for importation of cattle-derived protein meal from a country, zone or compartment posing a negligible BSE risk

Current Article 11.4.13. was revised consistent with the change in definition presented in section 4 of this report (i.e., from “meat-and-bone meal or greaves” to “protein meal”).

The Group recommended revising the scope from “ruminant-derived meat-and-bone meal or greaves” to “cattle-derived protein meal” as cattle (*Bos taurus* and *B. indicus*) are the species of relevance for BSE as defined in draft Article 11.4.1. Furthermore, as stated in draft Article 11.4.1., the recommendations in this chapter are intended to mitigate the human and animal health risks associated with the presence of the BSE agents in cattle only. As a result, the recommendations in draft Articles 11.4.6. to 11.4.18. are all about mitigating the BSE risks associated with the trade of commodities derived from cattle. Including “ruminants” more broadly in draft Article 11.4.14. would be beyond the scope of the BSE Chapter. It’s worth noting that Article 14.8.11., concerning scrapie, recommends to not trade MBM containing any sheep or goat protein from countries not considered free from scrapie, and does not impose restrictions for trade of ruminant-derived MBM.

Consistent with the revision proposed in draft Article 11.4.6., the Group recommended revising current Article 11.4.13. point 1. which provides recommendations for importation from negligible BSE risk countries where there has been an indigenous case of BSE. Indeed, provisions regarding the occurrence of an indigenous case of BSE, in a country, zone or compartment posing a negligible BSE risk were no longer considered relevant in light of the provisions of draft Article 11.4.3. The Group emphasised that the age of the cattle should be taken into consideration to ensure that they were born during the period when the likelihood of the BSE agent being recycled in the cattle population was assessed to be negligible.

The Group discussed whether recommendations could be developed for the importation of cattle-derived protein meal from countries, zones or compartments posing a controlled or undetermined BSE risk provided these protein meals are free from those commodities listed in draft Article 11.4.14. that are associated with the vast majority of BSE infectivity. However, the Group determined that the proper implementation of this requirement would be difficult to verify and stressed that the BSE risk associated with any improper implementation of this requirement would be significant considering the importance of protein meal in the recycling of BSE. The Group therefore concluded that it was not appropriate to develop recommendations for the importation of cattle-derived protein meal from countries, zones or compartments posing a controlled or undetermined BSE risk.

5.14. Draft Article 11.4.13. (New Article). Recommendations for importation of blood and blood products

Considering that the Group recommended that blood and blood products should no longer be listed as safe commodities (see section 5.2. of this report and draft Article 11.4.1.bis.) to comply with the recently adopted Chapter 2.2. of the *Terrestrial Code*, the Group drafted a new article to provide recommendations for the importation of blood and blood products.

The Group clarified that the provisions in this Article relate to blood and to blood products rather than to blood by-products. A blood by-product refers to one that is not intended to be produced but that results from processing of blood when a different final product is intended (which would be a blood product). Blood product refers to derived product from blood, which, together with blood are the scope of this Article.

The recommendations provided for blood and blood products derived from ruminants which were not born in a country, zone or compartment posing a negligible BSE risk during the period when the likelihood of the BSE agent being recycled in the cattle population has been demonstrated to be negligible ensure that cross contamination with nervous tissue is avoided.

5.15. Draft Article 11.4.14. Recommendations regarding commodities associated with the vast majority of BSE infectivity

The Group considered the recommendation made by the *ad hoc* Group on BSE which met in August 2016 proposing that the restriction applicable to tonsils be removed and reviewed the scientific evidence⁶ supporting this proposal. The Group concurred with the *ad hoc* Group that the restriction applicable to tonsils should be removed.

As emphasised in section 5.12. of this report, the Group agreed that current scientific evidence does not support an age limit of 12 months. The Group therefore recommended removing point 3. of current Article 11.4.14.

Consistent with current Article 11.4.13. point 2., and with the rationale presented in section 5.13. of this report, the Group emphasised that cattle-derived protein meal, or any commodities containing such products, which originate from a country, zone or compartment posing a controlled or undetermined BSE risk should not be traded. Therefore, the Group proposed to move this recommendation to draft Article 11.4.14. point 3.

The Group reviewed the recommendation made by the *ad hoc* Group on BSE which met in August 2016 proposing that the commodities “*from cattle that were at the time of slaughter over 60 or 72 months of age originating from a country, zone or compartment defined in Article 11.4.3., the following commodities, and any commodity contaminated by them, should not be traded for the preparation of food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices: brains, eyes, spinal cord and skull. Protein products, food, feed, fertilisers, cosmetics, pharmaceuticals or medical devices prepared using these commodities (unless covered by other Articles in this chapter) should also not be traded.*” This provision and age limit were proposed to mitigate the risk associated with atypical BSE. Consistent with the rationale presented in section 5.10. of this report, the Group determined that the proposal made by the *ad hoc* Group in 2016 was disproportionate to the level of risk and did not endorse it.

5.16. Draft Article 11.4.15. Recommendations for importation of gelatine and collagen prepared from bones and intended for food or feed, cosmetics, pharmaceuticals including biologicals, or medical devices

The Group reviewed the steps that bones should be subjected to for the preparation of gelatine and collagen as described in current Article 11.4.15. point 2.b. The Group considered a report from EFSA⁷ and agreed that the steps listed in point 2.b. were sufficient to ensure that “*the relative human exposures due to gelatine produced from bones including the skull and vertebral column sourced from cattle of any age are very low (< 10⁻⁵) and do not support the continuation of the restriction prohibiting the inclusion of skull and vertebral column*”. The Group therefore determined that the provision of exclusion in current Article 11.4.15. point 2.a. (i.e., “*vertebral columns from cattle over 30 months of age at the time of slaughter and skulls have been excluded*”) could not be justified.

⁶ EFSA Panel on Biological Hazards. Scientific Opinion on the revision of the quantitative risk assessment (QRA) of the BSE risk posed by processed animal proteins. *The EFSA Journal*. 2011; **9**(1):1947 doi:10.2903/j.efsa.2011.1947. The infectivity of tonsils is estimated to be <0.01% of the total amount of infectivity represented by the different tissues of a clinical case. The EFSA report cites the level of infectivity in tonsils to be 10^{-6.5} CoID₅₀/g, which is in the same order of magnitude as that for the peripheral nervous system (PNS). Such levels of infectivity are extremely low, so low that it would be in fact biologically implausible to ingest a sufficient amount of tissue from an infected animal to pose a credible risk. This has been widely accepted for the PNS and it is not classified as a high risk tissue. As a result, it is reasonable to conclude that the risk posed by tonsillar tissue is insignificant.

⁷ EFSA Panel on Biological Hazards. Opinion of the Scientific Panel on biological hazards (BIOHAZ) on the “Quantitative assessment of the human BSE risk posed by gelatine with respect to residual BSE [1]”. *The EFSA Journal*. 2006; **4**(1):312, 1–29 doi:10.2903/j.efsa.2006.312

Furthermore, the Group considered that the steps of the process described in point 2.b. were common industrial practices and were not specifically directed against BSE. Therefore, the Group contemplated whether, in light of the definition of safe commodities provided in the Glossary of the *Terrestrial Code* and of the provisions of Chapter 2.2. of the *Terrestrial Code*, gelatine and collagen prepared from bones and intended for food or feed, cosmetics, pharmaceuticals including biologicals, or medical devices could be considered safe commodities provided they are subjected to the processes currently described in point 2.b. of Article 11.4.15. After seeking advice from the Code Commission, the Group remained uncertain whether or not this would be fully consistent with Chapter 2.2. As a result, the Group proposed to maintain this provision in draft Article 11.4.15. at this stage and to refer the proposal to include it in the list of safe commodities to the Code Commission for further deliberation.

The Group reviewed the recommendation made by the *ad hoc* Group on BSE which met in August 2016 proposing that the commodities should come from a country, zone or compartment posing a negligible BSE risk and should be derived from cattle which have passed *ante-* and *post-mortem* inspections and the skull from cattle over 60 or 72 months of age at the time of slaughter should be excluded. Consistent with the rationale presented in section 5.10. of this report, the Group determined that this proposal was disproportionate to the level of risk and did not endorse it.

5.17. Draft Article 11.4.16. Recommendations for importation of tallow (other than as defined in Article 11.4.1.bis) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

The Group considered the opinion of the *ad hoc* Group on BSE that met in August 2016 which recommended that tallow coming from a country, zone or compartment posing a negligible BSE risk should not have been prepared using tissues listed in current Article 11.4.14. Consistent with the rationale presented in section 5.10. of this report, the Group determined that this proposal was disproportionate to the level of risk and did not endorse it.

The Group reviewed a recent study undertaken by Fast *et al.*⁸ where BSE infectivity was detected in tallow produced by standard rendering methods (20 minutes at 95° C) using mesentery with embedded nervous tissue from the celiac and mesenteric ganglion complex from a clinical case of classical BSE that had been experimentally infected by the oral route. While this provides proof of principle that prion infectivity in adipose tissue is associated with the nervous tissue attached to the mesentery, it is important to note that the level of infectivity (tested by transgenic mouse bioassay) was extremely low with positive findings in only 1 out of 6 mice. This indicates that the levels of infectivity would likely have been less than that detected in semitendinosus muscle where 9 out of 13 transgenic mice were positive (Kaatz *et al.*, 2012⁹). In the latter study, the level of infectivity was estimated to be at least 6 logs less than the brain. In light of these findings, the Group was of the opinion that the level of infectivity in tallow derived from mesenteric fat would be negligible.

The Group agreed that, based on the evidence available to date, the exclusion of those materials listed in point 1. of draft Article 11.4.14. in the preparation of tallow, ensures the effective mitigation of potential BSE risks regardless of whether the country, zone or compartment of origin has controlled or undetermined BSE risk status. As a result, the Group proposed to remove the specific reference to controlled BSE risk in point 2 of current Article 11.4.16. With this change, tallow would be eligible for trade from a country, zone or compartment posing a controlled or undetermined BSE risk as long as it derived from cattle that passed *ante-mortem* inspection and had not been prepared using the commodities listed in point 1 of draft Article 11.4.14.

⁸ Fast C, Keller M, Kaatz M, Ziegler U, Groschup MH. Low levels of classical BSE infectivity in rendered fat tissue. *Veterinary Research*. 2018; **49**(1):122.

⁹ Kaatz M, Fast C, Ziegler U, Balkema-Buschmann A, Hammerschmidt B, Keller M, Oelschlegel A, MacIntyre L, Groschup MH (2012) Spread of classic BSE prions from the gut via the peripheral nervous system to the brain. *Am. J. Pathol.*, **181**:515–524.

5.18. Draft Article 11.4.17. Recommendations for importation of dicalcium phosphate (other than as defined in Article 11.4.1.bis) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

As dicalcium phosphate can be considered a co-product of bone gelatine, the Group concurred with the opinion of the *ad hoc* Group on BSE which met in August 2016 which recommended that dicalcium phosphate should originate from products compliant with the requirements of the relevant article within Chapter 11.4. (i.e., draft Article 11.4.15.). However, the Group emphasised that this provision should only apply to countries, zones, or compartments posing a controlled or undetermined BSE risk.

Furthermore, the Group clarified that dicalcium phosphate is rather a co-product than a by-product of bone gelatine as it is produced along with gelatine when the material of origin is bone. Both gelatine and dicalcium phosphate share the initial production steps (i.e., decreasing and demineralization) and are both intended outputs of the process.

5.19. Draft Article 11.4.18. Recommendations for importation of tallow derivatives (other than those made from tallow as defined in Article 11.4.1.bis) intended for food, feed, fertilisers, cosmetics, pharmaceuticals including biologicals, or medical devices

The Group considered the provisions of current Article 11.4.18. point 3. which recommend that tallow derivatives should have been produced by hydrolysis, saponification or transesterification using high temperature and pressure. The Group considered that these measures were common industrial practices and were not specifically directed against BSE. Therefore, the Group contemplated if in light of the definition of safe commodities provided in the Glossary of the *Terrestrial Code* and of the provisions of Chapter 2.2. of the *Terrestrial Code*, tallow derivatives could be considered safe commodities provided they are subjected to the process described in current Article 11.4.18. point 3. However, after receiving preliminary advice from the Code Commission, the Group proposed to maintain the corresponding provision in draft article 11.4.15. at this stage, and to refer the proposal to include it in the list of safe commodities to the Code Commission for further consideration.

5.20. Draft Article 11.4.19. Procedures for the reduction of BSE infectivity in protein meal

The Group did not propose any revision to the procedures for the reduction of BSE infectivity in protein meal.

5.21. Draft Article 11.4.20. Passive surveillance

The Group reviewed and endorsed the revised Article on BSE surveillance drafted by the *ad hoc* Group on BSE surveillance in October 2018 and made only minor editorial changes.

6. Revision of Chapter 1.8. of the *Terrestrial Code*

The Group reviewed and edited draft Chapter 1.8. (the BSE “questionnaire”) which was only initially drafted by the *ad hoc* Group on BSE risk assessment at its November 2018 meeting and completed electronically by the experts ahead of this meeting. Major edits in the structure of the BSE questionnaire were done to ensure full consistency between this document and revised Chapter 11.4.

6.1. General considerations

At its November 2018 meeting, the *ad hoc* Group on BSE risk assessment did not reach a consensus regarding whether or not applicant Members should undertake and document a BSE risk assessment, or alternatively, if the BSE “questionnaire” should facilitate the compilation of sufficient data to enable the *ad hoc* Group on BSE Risk Status Evaluation of Members to undertake the BSE risk assessment. The Group discussed these options and agreed that applicant Members should document the necessary body of

evidence and undertake the risk assessment. In addition, the Group recommended that likelihood estimates for each step of the risk assessment process as well as the final risk estimate should be consistent with and based on the guidance provided in the OIE *Handbook on Import Risk Analysis for Animals and Animal Products*.

The Group acknowledged that “questionnaires” for the official recognition of status for other diseases (i.e., Chapters 1.7. and 1.9. to 1.12.) do not justify why certain information is necessary nor offer detailed guidelines on how it should be provided. However, the Group was of the opinion that applicant Members for the official recognition of a BSE risk status would benefit from detailed guidance to assist them in undertaking a comprehensive risk assessment. Furthermore, the Group was of the opinion that Chapter 1.8. should, as much as possible, be designed to be a “user friendly”, standalone document without extensive cross-references to other Chapters of the *Terrestrial Code*.

Consistent with the recommendations for trade applicable to various commodities, applicant Members would have the option of providing evidence for a different period of time (more than eight years if applying for negligible risk status, or for the time they have it if applying for a controlled risk status) in support of a determination, by the *ad hoc* Group on BSE Risk Status Evaluation of Members, of the actual period when the likelihood of the BSE agent being recycled in the cattle population has been assessed to be negligible. See sections 5.7. and 5.8. of this report.

6.2. Draft Article 1.8.5. point 1. Entry assessment

Based on the experience of the OIE *ad hoc* Group on BSE Risk Status Evaluation of Members, applicant Members tend to provide extensive amounts of data, information, tables, and figures in their applications which do not necessarily inform the risk assessment. The Group re-affirmed its previous position that detailed quantitative information (e.g., volume, statistics, etc.) on imported commodities was not informative for the entry assessment as long as either the commodities were imported under conditions consistent with the recommendations laid out in Chapter 11.4. or it can be demonstrated that an equivalent level of assurance was provided. The emphasis should be on documenting the measures applied to imported commodities depending on the BSE risk status of the country or zone of origin together with how the Competent Authority verifies compliance through supporting legislation, certification, and regulations.

6.3. Draft Article 1.8.5. point 2. Exposure assessment

The Group discussed how an applicant Member should determine which pathway (i.e., either livestock industry practices or effective and continuous mitigation of each identified risk) to follow during the application for official recognition of its BSE risk status. The Group indicated that it would be based on the conclusions arising from livestock industry practices and the associated likelihood that the cattle population has been exposed to either classical or atypical BSE agents. If the applicant Member concluded that the likelihood has been non-negligible, an evaluation of BSE specific mitigation measures should be performed. The Group agreed that the applicant should provide information on livestock industry practices regardless of the pathway chosen as this provides indispensable background information.

If an applicant Member concluded that the likelihood that the cattle population has been exposed to either classical or atypical BSE agents has been negligible as a result of its livestock industry practices, but the *ad hoc* Group on BSE Risk Status Evaluation of Members reached a different conclusion, the application for a BSE risk status would be rejected. The applicant Member would then be invited to apply for the recognition of its BSE risk status based on the effective and continuous mitigation of each identified risk.

Current Article 11.4.2. point 1.b. recommends that “*if the entry assessment identifies a risk factor, an exposure assessment should be conducted*”. Consistent with the provisions of draft Article 11.4.2., the Group stressed that in the revised framework for BSE, an exposure assessment should be undertaken regardless of the outcome of the entry assessment. Indeed, in accordance with the findings of the overview on “*Atypical BSE: the risk of being recycled in a cattle population and its zoonotic potential*” (section 3 of this report and Appendix IV), the potential recycling of atypical BSE in any cattle population should be considered and, if necessary, mitigated.

6.4. Draft Article 1.8.5. point 3. Consequence assessment

The Group explained the circumstances that could lead to the recycling of BSE agents in a cattle population. In particular, the Group outlined the series of events that could initiate a cycle of BSE infectivity within a cattle population and made clear that recycling would arise when this cycle is repeated one or more times.

The Group emphasised that any level of recycling within a given period was sufficient to conclude that the consequences of exposure to contaminated feed for that period within the cattle population was non-negligible.

6.5. Draft Article 1.8.5. point 4. Risk estimation

The risk estimation is the final step of the BSE risk assessment, and should provide an overall measure of the risk that the BSE agents have been recycled in the cattle population through the feeding of cattle with ruminant-derived protein meal, with indigenous cases arising as a consequence.

6.6. Draft Article 1.8.6. BSE surveillance

Current Article 1.8.4. on BSE surveillance was revised to reflect the new provisions for BSE surveillance defined in draft Article 11.4.20.

6.7. Draft Article 1.8.7. Recovery of a BSE risk status

The Group provided some guidance for Members applying for the recovery of a previously recognised negligible BSE risk status suspended following non-compliance with any of the 4 provisions of Article 11.4.3, including the occurrence of an indigenous case of classical BSE in an animal born within the preceding 8 years.

7. Potential impact of the revision of the BSE standards on the official BSE risk status currently recognised

Based on the provisions of draft Chapter 11.4. an exposure assessment should be undertaken regardless of the outcome of the entry assessment. However, in accordance with the provisions of current Chapter 11.4. (Article 11.4.2. point 1.b.), some Members have had an official BSE risk status recognised by the OIE based on a negligible likelihood of entry despite a non-negligible likelihood of exposure at the time of the assessment.

The OIE Secretariat pre-identified 18 Members which may be impacted by the revision of the BSE standards, if a negligible likelihood of exposure cannot be demonstrated.

The Group agreed that updated information should be gathered on the likelihood of exposure to the BSE agents, including through the 2019 annual reconfirmation campaign as necessary. The Group recommended that based on the updated information collected, the likelihood of exposure to the BSE agents should be (re)assessed under the responsibility of the Scientific Commission with the support of the *ad hoc* Group on BSE Risk Status Evaluation of Members if necessary.

If based on the updated assessment, the likelihood of exposure is assessed to be non-negligible for some Members, the Scientific Commission would have to determine how the recognised status would be impacted. The Group emphasised that the BSE risk posed by a Member's cattle population has not changed as a result of the proposed changes to the Chapter and a pragmatic approach would be required to ensure against any disproportionate impact on individual Members.

8. Retention on the list of negligible or controlled BSE risk status

The Group discussed the level of evidence that should be provided by Members annually to confirm compliance with the relevant provisions of draft Articles 11.4.3. and 11.4.4. to be retained on the list of countries or zones with negligible or controlled BSE risk status.

The Group advised that Members should annually:

- confirm that the risk assessment for BSE has been reviewed indicating whether or not the conclusion has changed and when it has, provide the updated risk assessment to the OIE;
- provide documented evidence that passive surveillance for BSE has been implemented in accordance with the provisions of draft Article 11.4.20;
- confirm that there have not been any cases of classical BSE in indigenous cattle born less than 8 years ago;
- confirm, in addition to the information provided through notifications made in accordance with the requirements of Chapter 1.1. of the *Terrestrial Code*, that any BSE cases detected have been completely destroyed or disposed of.

The Group agreed that based on these provisions, an annual reconfirmation form would be drafted by the OIE Secretariat and circulated to the Group for its review.

In addition, to increase confidence in the annual review of the BSE risk assessment and its conclusions, the Group suggested that Members could be requested to provide an updated risk assessment either at a given frequency (e.g., every 10 years), or when selected for comprehensive review by the Scientific Commission (i.e., 10% of the official BSE risk status each year). The Group recommended this proposal be referred to the Scientific Commission for its consideration.

9. Recommendations for the consideration of the OIE

The Group recommended the overview on “*Atypical BSE: the risk of being recycled in a cattle population and its zoonotic potential*” (Appendix IV) be referred to the Biological Standards Commission in support of the update of Chapter 3.4.5. of the *Terrestrial Manual* (section 5.1. of this report). The Group also recommended that consistency should be ensured between the list of behavioural or clinical signs related to BSE defined in draft Article 11.4.20. and those listed in Chapter 3.4.5. of the *Terrestrial Manual*.

The Group recommended that when assessing applications for the recognition of a BSE risk status, the ad hoc Group on BSE Risk Status Evaluation of Members should specify the date from which likelihood of the BSE agent being recycled in the cattle population is assessed to be negligible. This period could be longer than 8 years for Members applying for a negligible risk status, or for the time there is sufficient evidence for Members applying for a controlled risk status (sections 5.7. and 5.8. of this report).

The Group noted that whether the definition of “protein meal” proposed for the purpose of Chapters 11.4. and 1.8. is relevant for other disease-specific Chapters (i.e., Chapter 8.1. on anthrax; Chapter 8.4. on infection with *Brucella abortus*, *B. melitensis* and *B. suis*; Chapter 8.11. on infection with *Mycobacterium tuberculosis complex*; Chapter 14.8. on scrapie; and Chapter 15.3. on infection with porcine reproductive and respiratory syndrome virus) should be further assessed by the OIE. See Section 4 of this report.

The Group recommended that the following commodities be further considered by the Code Commission for inclusion as safe commodities:

- gelatine and collagen prepared from bones subjected to the process described in draft Article 11.4.15. point 2. and intended for food or feed, cosmetics, pharmaceuticals including biologicals, or medical devices (section 5.16. of this report); and
- tallow derivatives produced by hydrolysis, saponification or transesterification using high temperature and pressure (section 5.19. of this report).

The Group recommended that the potential impact of revisions of the BSE standards on the currently recognised BSE risk status should be further assessed by the Scientific Commission with the support of the *ad hoc* Group on BSE Risk Status Evaluation of Members as necessary. See section 7 of this report.

The Group emphasised that training by the OIE on the procedures and requirements for the official recognition of the BSE risk status of a country or zone would be beneficial for Members upon the adoption of the revised provisions.

The Group noted that due to the nature of BSE, OIE standards are likely to need to be reassessed in the future in light of emerging scientific evidence and the evolution of the global situation for BSE.

10. Finalisation and adoption of the report

The Group reviewed and amended the draft report. The Group agreed that the report reflected the discussions.

.../Annexes

Annex I**MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY
RISK ASSESSMENT AND SURVEILLANCE****Paris, 18-21 March 2019****Terms of Reference****Purpose**

The purpose of this *ad hoc* Group is to provide independent analysis and advice to OIE on the surveillance and risk-based provisions applicable to the recognition and maintenance of BSE risk status as well as on recommendations applicable for international trade.

Functions

This *ad hoc* Group will report to the Director General of the OIE, and approved reports will be considered by the relevant Specialist Commissions (the Scientific Commission or the Terrestrial Animal Health Standards Commissions) when necessary, in accordance with the OIE Basic Texts.

- Experts' contributions will be solicited in preparation of this meeting under the coordination of the OIE Secretariat.
- During this meeting, this *ad hoc* Group will:

1. Finalise the revision of Chapter 11.4.:

a. Further consider atypical BSE, including:

- Review and endorse a draft paper on the risk of atypical BSE being recycled in a cattle population and its zoonotic potential;
- Ensure that the terms 'atypical', 'classical', and 'BSE agent(s)/strains' are clearly stated to avoid ambiguity about the applicability of each provision to either atypical BSE only, classical BSE only, or both, in Chapters 1.8. and 11.4., and in the annual reconfirmation form.

b. Article 11.4.3. (Negligible BSE risk), considering in particular:

- whether the need for a Member to demonstrate the implementation of a ruminant-to-ruminant feed ban should be explicitly stated as an independent point (point 1.b.) (i.e., a separate point to the provision on risk assessment) or if it would be sufficient to rather implicitly consider it within the risk assessment (point 1.a.) (i.e., by indicating that the risk assessment should demonstrate a negligible likelihood of recycling);
- proper wording to clearly state that if there has been an indigenous case of classical BSE in an animal born 8 or less years ago in a country or zone already recognised with a negligible BSE risk status, the Member could retain the status as long as an investigation confirms that the likelihood of the BSE agent being recycled within the cattle population remained negligible (point 2.b.ii.).

c. Articles 11.4.6. to 11.4.19 (recommendations for trade commodities) taking into consideration the proposals made by the *ad hoc* Group on BSE which met in August 2016;d. Article 11.4.1. (safe commodities) taking into consideration the proposals made by the *ad hoc* Group on BSE which met in August 2016 as well as the recent scientific knowledge;

- e. Article 11.4.14. (commodities that should not be traded) taking into consideration the proposals made by the *ad hoc* Group on BSE which met in August 2016, the opinion of the Scientific Commissions on these proposals, as well as the recent scientific knowledge;
 - f. Article 11.4.20. (BSE Surveillance).
2. Finalise the revision of Chapter 1.8. (BSE questionnaire):
- a. Address any remaining matters based on comments to the Draft Questionnaire. In particular:
 - Determine whether the BSE risk assessment should be performed by the applicant Member or by the *ad hoc* Group on BSE risk status evaluation of Members. This will impact the type, amount and granularity of the data and information to be included in the questionnaire.
 - Clarify BSE risk status recognition of compartments.
 - Agree on the steps to follow after a pathway for achieving negligible risk status is selected and how to reflect this on the Questionnaire. Should information on specific risk mitigation measures be provided after selecting the first pathway (i.e., livestock industry practices)?
 - Agree whether a ruminant-to-ruminant feed ban is compulsory regardless of its presence or absence in a country's legislation.
 - b. Discuss whether an Article on Conclusions is needed.
 - c. Ensure full consistency between the questionnaire and draft revised Chapter 11.4.
3. Address any remaining issues, including:
- a. Review the definitions of meat-and-bone meal and greaves within Chapters 1.8. and 11.4. and assess whether updated definitions should be proposed and whether the revised definitions would only apply to Chapters 1.8. and 11.4., or throughout the *Terrestrial Code* (i.e., revision of the Glossary).
 - b. Assess the impact of the proposed revised requirements for the categorisation of BSE risk status on the countries or zones already having an officially recognised BSE risk status.
 - c. Revise the form in support of the annual reconfirmation of BSE risk status
 - Ensure full consistency between the reconfirmation form and draft revised Chapter 11.4.
 - d. Consider a request from the European Serum Products Association.
- Should the Group not be able to complete its Terms of reference during this meeting, experts' contributions will be solicited after the meeting, including by teleconference(s) if needed.
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Annex II

**MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY
RISK ASSESSMENT AND SURVEILLANCE**

Paris, 18-21 March 2019

Agenda

1. Opening
 2. Adoption of the agenda and appointment of chairperson and rapporteur
 3. Atypical BSE
 4. Definitions of meat-and-bone meal (MBM) and greaves
 5. Revision of Chapter 11.4. of the *Terrestrial Code*
 6. Revision of Chapter 1.8. of the *Terrestrial Code*
 7. Potential impact of the revision of the BSE standards on the official BSE risk status currently recognised
 8. Recommendations for the consideration of the OIE
 9. Retention on the list of negligible or controlled BSE risk status
 10. Finalisation and adoption of the report
-

**MEETING OF THE OIE AD HOC GROUP ON BOVINE SPONGIFORM ENCEPHALOPATHY
RISK ASSESSMENT AND SURVEILLANCE**

Paris, 18-21 March 2019

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Annex IV**Atypical bovine spongiform encephalopathy (BSE) – transmissibility among cattle and its zoonotic potential**OIE *ad hoc* Group on BSE risk assessment and surveillance – March 2019

This overview of relevant literature was prepared by Dr N. Murray on behalf of the OIE *ad hoc* Group on BSE risk assessment and surveillance, and was edited and endorsed by this *ad hoc* Group. It aims to gather current scientific literature to support the assessment of the risk of recycling of atypical BSE in a cattle population and its zoonotic potential to support an informed risk-based revision of the provisions for atypical BSE outlined in Articles 11.4.2. and 11.4.3. of the *Terrestrial Animal Health Code*.

I. Implications for the cattle population of a country (risk of recycling)

Atypical BSE is a neurological disease of cattle caused by misfolded prion proteins with different conformations than those of the classical BSE (C-BSE). Two phenotypes of atypical BSE have been recognised, designated H-type or L-type based on Western Blot characteristics of the unglycosylated PrP following proteinase-K (PK) digestion (Casalone *et al.*, 2004, Biacabe *et al.*, 2004), both are transmissible to cattle following intracerebral inoculation (Lombardi *et al.*, 2008; Fukuda *et al.*, 2009; Konold *et al.*, 2012; Balkema-Buschmann *et al.*, 2011; Okada *et al.*, 2011).

As discussed in a previous report from an OIE *ad hoc* Group on BSE (August 2016), epidemiological data from Europe as well as from Brazil, Canada, Israel, Japan and the United States of America (USA) all support the contention that atypical BSE is likely to arise spontaneously in all cattle populations at a very low rate.

Simmons *et al.* (2017) highlighted the fact that in experimental inoculation models in cattle, the incubation periods of H- and L-BSE were similar to or shorter than those observed with C-BSE (Balkema-Buschmann, Ziegler, *et al.*, 2011; Fukuda *et al.*, 2009; Konold *et al.*, 2012; Lombardi *et al.*, 2008). Based on pooled data for 110 atypical cases for which the age is known from the European Union (EU) and the OIE for countries outside the EU from 2001 to 2019, most cases (>91.7%) have been detected in animals 8 years or older¹⁰ (European Commission, 2016; EFSA 2016, 2017, 2018). The youngest case reported to date was almost 67 months old (5.6 years) (World Organisation for Animal Health, 2019).

In recently published research work, Okada and colleagues, 2017, confirmed that the L-type BSE prion can be orally transmitted. Of 16 calves challenged with various amounts of infectious brain material, only 1 animal, which was given a high dose (50 grams), developed clinical signs after a lengthy incubation period of 88 months (7.3 years). The rest of the calves (1 that received the same dose, and 15 that received lower doses) did not show clinical signs and results were negative by Western blot and immunohistochemistry analyses after 51-94 months post inoculation. Although this study is limited, its results suggest a low likelihood of oral transmission of L-BSE agent among calves. Moreover, based on the dose-response curve estimated by Wells *et al.* (2007), for a comparable amount of infectivity for C-BSE, the corresponding incubation period would be approximately 55 months, indicating that C-BSE would be more infectious.

In contrast, there have not been any substantiated reports of the successful oral transmission of H-BSE in cattle. Initial reports from Dudas *et al.*, 2014 based on RT-QuIC pointed to the possibility of oral transmission following a very high dose (100 grams of brain material), although the individual did not display clinical signs and the findings from standard molecular or immunohistochemical assays were all negative. Investigations are ongoing in an attempt to clarify these findings.

Although significant uncertainty remains regarding the origin of C-BSE, several studies involving the serial passage of H-BSE and L-BSE in transgenic and wild-type mice have revealed their potential to lead to the emergence of a C-BSE-like phenotype (Baron *et al.*, 2011; Torres *et al.*, 2011; Bencsik *et al.*, 2013) or other novel strains (Masujin *et al.*, 2016). Whether or not one or both of these atypical strains led to the emergence of C-BSE remains speculative; however, the similarities between transmissible mink encephalopathy (TME), first reported in the USA in 1947 (Hartsough and Burger, 1965), and L-BSE indicate that TME may have been a surrogate indicator for the presence of L-BSE in cattle populations in those countries such as the USA, Canada, Germany, Finland and Russia where outbreaks of TME had been reported decades before C-BSE was first recognised in the

¹⁰ Pulled data from 110 atypical cases: 49 H-BSE, 58 L-BSE and 3 of unknown atypical type. The mean age at diagnosis was 11.6 years (from 5.5 to 18 years). 78.2% were between 10 and 15 years old.

United Kingdom in 1986 (Hadlow and Karstad, 1968; Marsh *et al.*, 1991; McKenzie *et al.*, 1996; Baron *et al.*, 2007; Comoy *et al.*, 2013). Although TME was originally thought to have occurred as a result of feeding mink with scrapie infected sheep carcasses, oral challenge studies did not confirm this (Marsh *et al.*, 1991). Importantly, in an outbreak reported in the USA in 1985, mink had never been fed sheep products; instead they had been fed on products derived from dead and sick dairy cattle (March *et al.*, 1991). Similarly, from an outbreak in Canada in 1963, mink had reportedly been fed with products derived from cattle but not sheep (Hadlow and Karstad, 1968).

Although, as discussed above, the passage of H-BSE or L-BSE has been proposed as a possible explanation for the origin of C-BSE, transformation of L-BSE or H-BSE to C-BSE has not been observed so far in transmission studies in cattle. That being said, it is likely that, compared to various rodent models, an insufficient number of passages have been undertaken.

It is worth noting that sheep and goats are susceptible to L-BSE following intracerebral inoculation without lymphoid involvement in most individuals (Simmons *et al.*, 2016; Gielbert *et al.*, 2018; Vallino-Costassa *et al.*, 2018). As discussed by Houston and Andreoletti (2018), C-BSE appears to increase in virulence for humans if it is first passaged in sheep. Whether or not this is the same for atypical strains remains to be determined.

Conclusions on transmissibility of atypical BSE among cattle

Given that cattle have been successfully infected by the oral route, at least for L-BSE, it is reasonable to conclude that atypical BSE is potentially capable of being recycled in a cattle population if cattle are exposed to contaminated feed. In addition, based on reports of atypical BSE from several countries that have not had C-BSE, it appears likely that atypical BSE would arise as a spontaneous disease in any country, albeit at a very low incidence in old cattle. In the presence of livestock industry practices that would allow it to be recycled in the cattle feed chain, it is likely that some level of exposure and transmission may occur. As a result, since atypical BSE can be reasonably considered to pose a potential background level of risk for any country with cattle, the recycling of both classical and atypical strains in the cattle and broader ruminant populations should be avoided.

II. Zoonotic potential

Experimental studies

There are tremendous challenges in demonstrating the zoonotic transmission of atypical strains of BSE in natural exposure scenarios based on experimental studies involving:

- *In vivo* models including non-human primates (macaques and lemurs) (Comoy *et al.*, 2008; Ono *et al.*, 2011; Mestre-Frances *et al.*, 2012), humanised transgenic mice that either overexpress human PrP or express it at normal physiological levels (Béringue *et al.*, 2007; Béringue *et al.*, 2008; Kong *et al.*, 2008; Wilson *et al.*, 2012)
 - artificial routes of challenge such as intracerebral inoculation;
 - large doses of infectious material whether administered parenterally or orally.
- *In vitro* models including PMCA (protein misfolding cyclic amplification) reactions where brain homogenates from humans or transgenic mice containing PrP^c are used as a substrate (Barria *et al.*, 2014a; Barria *et al.*, 2014b);

In addition, not all studies are in agreement, for example:

- PMCA results suggest that atypical BSE poses a lower zoonotic risk than C-BSE since neither L-BSE nor H-BSE produced detectable human PrP^{res} when brain homogenates from humans or transgenic mice representative of human prion protein genotypes (codon 129 MM and VV) were used as substrates. In contrast, both C-BSE and variant Creutzfeldt-Jacob disease (vCJD) successfully converted human PrP^c to PrP^{res} in a codon 129 (M allele) dependent manner (Barria *et al.*, 2014a; Barria *et al.*, 2014b).
- Using humanized transgenic mice (tg650) overexpressing human PrP, H-BSE failed to transmit indicating the existence of a robust transmission barrier whereas the potential zoonotic risk from L-BSE appeared to be higher than C-BSE with attack rates on first passage of 100% and 30%, respectively. An attack rate of 100% for C-BSE was only achieved on third passage (Béringue *et al.*, 2008).
- Initial findings using transgenic mice expressing physiological levels of the human PrP representative of the three genotypes correlating with human susceptibility to TSEs (codon 129 MM, MV, VV) were suggestive of a significant transmission barrier between both L-BSE and H-BSE and humans (Wilson *et al.*, 2012). However, on subsequent passage into bovinized transgenic mice (Bov6), some of the mice originally challenged with L-BSE were found to harbour low levels of infectivity in their brains (Wilson *et al.*, 2013). Interestingly, in an earlier study, C-BSE was not transmitted to the same lines of humanized transgenic mice (Bishop *et al.*, 2006), whereas vCJD was successfully transmitted to all three lines. This is likely to be indicative of a significant cattle to human barrier for C-BSE, but a substantially reduced barrier for human-to-human transmission once that barrier is overcome. It is worth noting that an important limitation of these studies is the lifespan of mice that is much shorter than the incubation period of humans having only a single copy of the allele.
- Studies involving the intracerebral challenge of non-human primates (cynomolgus macaques) indicate that L-BSE is more virulent than C-BSE with shorter incubation periods (~20 months vs 38 months) (Comoy *et al.*, 2008; Ono *et al.*, 2011). While a similarly short incubation period was observed in mouse lemurs challenged through the oral route with L-BSE (Mestre-Frances *et al.*, 2012), transmission of C-BSE was only observed after initially being passaged in macaques (Bons *et al.*, 2002). This finding would also support the contention that L-BSE is more virulent than C-BSE. L-BSE has reportedly been transmitted to macaques by the oral route although a direct comparison with C-BSE does not appear to have been made (Comoy 2010; BIOHAZ, 2011). The results of this work have yet to be formally published (Comoy E, pers comm, 2019).

Tissue distribution of atypical BSE in cattle

The uncertainty associated with the actual route of acquiring the disease, if any, limits the implementation of appropriate studies investigating the pathogenesis of atypical BSE and the accumulation, progression and detection of PrP^{Sc} and infectivity in different tissues. Nevertheless, a limited number of studies have been undertaken (Appendix A of EFSA, 2014). PrP^{res} has been detected in the peripheral nervous system (PNS) of cattle intracerebrally inoculated with L-BSE (Iwamaru *et al.*, 2010) and H-BSE (Okada *et al.*, 2013) as calves. As with C-BSE, PrP^{res} from animals challenged with L-BSE was found to accumulate in both central and peripheral nerve tissues in a time-dependent manner suggesting that propagation was initially in the central nervous system (CNS) followed by spread into the PNS (Iwamaru *et al.*, 2010). The levels of infectivity in the PNS were approximately 1,000 times lower than those in the CNS. PrP^{res} was not detected in lymphoid tissues. Infectivity was detected in the skeletal muscle from a 14-year-old natural case of L-BSE as well as from an experimentally infected cow that had been inoculated intracerebrally as a calf (Suardi *et al.*, 2012). In this study, infectivity was not found in the spleen, cervical lymph nodes or kidneys of either the natural or experimentally infected cows.

Potential link between atypical BSE and sporadic Creutzfeldt-Jacob disease (sCJD)

It has been reported that the biochemical signature of L-BSE in an intracerebrally inoculated macaque was similar to that of the MM2 cortical subtype of human sCJD (Comoy *et al.*, 2013) raising the possibility that if L-BSE crossed the species barrier into humans it could present as sCJD. In a study involving humanized transgenic mice, Kong *et al.*, 2008, also reported that similarities between L-BSE and sCJD where the electrophoretic pattern of L-BSE and that of Type 2 PrP^{res} from sCJD patients were indistinguishable. The possibility that the two diseases are causally linked was subsequently investigated by Jaumain *et al.*, 2016, who compared the phenotypic traits of

L-BSE isolates with those from representative human sCJD cases. Although evidence of an aetiological link was not found, they nevertheless cautioned that an unrecognised form of CJD may emerge from the accidental transfer of L-BSE to humans.

Conclusions on the zoonotic potential of atypical BSE

Given the findings to date, the associated uncertainties and challenges in drawing inferences from studies involving surrogate models such as non-human primates, transgenic mice and molecular techniques, some tentative conclusions can nevertheless be drawn that inform potential zoonotic risks:

- While L-BSE poses a potentially greater zoonotic risk than C-BSE, the risk associated with H-BSE is likely to be less.
- Consistent with C-BSE, both H and L-BSE are likely to be essentially restricted to the CNS with involvement of the PNS at substantially lower levels arising later in the disease process.
- It is highly unlikely that lymphoid and other tissues outside the CNS and PNS are involved in the pathogenesis of H and L-BSE.
- It would be reasonable to assume based on the limited evidence available to date that the distribution of atypical BSE is similar to C-BSE with the exception of the distal ileum and tonsils.
- Potential human exposure to atypical BSE would be by the oral route that is unlikely to be repeated at an individual level considering that atypical BSE is a rare disease that is likely to arise spontaneously in old cattle.
- If atypical BSE were to break the species barrier, a form of CJD may emerge with the potential for a substantially reduced barrier for subsequent human-to-human transmission.
- Although the likelihood of human exposure to atypical BSE with the species barrier being breached may be considered to be extremely low, the consequences as experienced with C-BSE would be high if exposure results in infection.

At this stage it would be premature to reach a conclusion other than that atypical BSE poses a potential zoonotic risk that although may be different between atypical strains, nevertheless justifies a consideration of measures to prevent recycling in the cattle population to protect both the human food supply and the ruminant feed chain.

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