

United States Comments

Terrestrial Animal Health Standards Commission Report - March 2008

CHAPTER 2.4.8.

SCRAPIE

The United States is unable to support the proposed new draft Code Chapter on Scrapie. The draft chapter, as written, departs significantly from the existing chapter, is confusing and is difficult to understand. This version of the scrapie chapter uses much of the same wording as the BSE chapter and is written as if the predominance of evidence revealed that scrapie was a food-borne disease similar to BSE in cattle which is inappropriate. Moreover, several of the new changes are not supported by current scientific evidence. As a result, detailed comments on individual articles would not be meaningful at this time.

The United States is not supportive of the proposed draft chapter for the following reasons:

1. **Inclusion of “atypical” scrapie:** The scientific evidence indicates that “atypical” scrapie, also referred to as Nor-98, Nor-98-like, or non-classical scrapie, is not the same disease as classical scrapie. Further, “atypical” scrapie does not meet the criteria for listing diseases of trade concern by the OIE, as described in *Chapter 2.1.1* of the *Code*.

The United States recommends that the scope of this chapter be limited to classical scrapie in sheep and goats. Further, the United States recommends that OIE clearly adopt the position that “atypical” scrapie represents a distinct disease entity from classical scrapie and that it not be a listed disease.

- There is no evidence that “atypical” scrapie is a contagious disease. If it is contagious, available evidence suggests that it has a much lower transmission efficiency. (Hopp, et al, 2006; Green, et al, 2007; Benestad, et al 2008; McIntyre, et al, 2008)
- The disease appears to be ubiquitous in that it has been found wherever sufficient surveillance has been conducted. (Buschmann et al, 2004; De Bosschere et al, 2004; Orge, et al, 2004; Everest et al, 2006; Arzac, 2007; Benestad, et al 2008; Fediaevsky, et al, 2008)
- The disease does not appear to be economically significant in that the prevalence of clinical disease is low and it typically occurs in older animals. (Luhken, et al., 2007; Benestad, et al 2008).
- The disease is as likely as not to be the result of a spontaneous conversion of normal prion protein. (Benestad, et al 2008, De Bosschere et al 2007)
- Removal of exposed sheep is unlikely to reduce the prevalence of “atypical” scrapie infection and removing only those exposed sheep that are phenylalanine (F) at codon 141 is scientifically unsound since the disease is known to affect sheep of most other genotypes. Further, sheep with AHQ alleles have a similar risk of infection with “atypical” strains as sheep with F at codon 141. (Luhken, et al., 2007).
- If “atypical” scrapie is included as a listed disease, the surveillance and diagnostic requirements which are needed to identify these cases should be described in detail in both this Chapter and the Manual of Diagnostic Tests and Vaccines for Terrestrial

Animals. Data from Europe illustrates that using the proper test(s) is essential for the identification of atypical scrapie (Fediaevsky et al., 2008).

2. **Failure to adequately consider the scrapie status of the importing country:** The United States believes that the scrapie status of the importing country is an equally important consideration with respect to the development of the guidelines contained within this draft chapter. However, the current draft only considers the scrapie status of the exporting country.

The United States recommends that more robust risk mitigations be set for imports by scrapie-free and scrapie-negligible risk countries, and for countries actively working toward negligible risk.

- The potential impacts of scrapie introduction as a result of the importation of sheep and goats or their products are significantly different between scrapie free or negligible risk countries (or those actively working to achieve this status) and those where scrapie is known to exist.
 - The former need to virtually eliminate the risk of importing scrapie because of the substantial economic impact of either losing negligible risk status or failing to achieve eradication after a substantial investment of resources; whereas the latter need only mitigate the risk since the impact of importing a rare case is not significantly different from the identification of a domestic case.
 - In countries with an indigenous case of classical scrapie, the scrapie agent is likely to be present in meat and bone meal (MBM) or other protein containing materials derived from sheep and goats as well as other processed animal proteins handled in the same facilities. The scrapie agent would likely be present in these materials **regardless** of the presence of a feed ban and/or a SRM policy. As scrapie can be transmitted through feed with subsequent lateral transmission among animals, this chapter should be worded to prevent the importation by negligible risk countries and countries working toward negligible risk such materials that are intended for or likely to be used in animal feed from countries that are not negligible risk.
 - It is well documented that the spread of scrapie around the world correlates to imports and exports (Detwiler and Baylis, 2003). The Chapter should provide more emphasis in regard to the movement, tracking, and deposition of imported sheep especially from countries known to have scrapie.
 - Controlled risk countries should be able to trade animals and products between themselves, if they wish to do so, without losing controlled risk status. Likewise, countries should have the option of utilizing additional mitigations such as excluding susceptible genotypes, requiring live animal lymphoid tissue biopsy testing of susceptible animals prior to importation, and/or a risk assessment regarding the risk of importing foreign classical scrapie strains, if necessary, to ensure their success in maintaining a low scrapie prevalence or in reducing scrapie prevalence.
3. **Failure to recognize “strain” variation of classical scrapie between countries:** The United States believes that the genetic-based control strategies outlined in this proposed chapter over-emphasize the significance of valine-dependent strains of classical scrapie, and fail to provide countries with adequate safeguards pertaining to other known classical strains.

The United States recommends that risk assessments consider and mitigation strategies be based on the likelihood of exposure to strains of classical scrapie that do not currently exist in the importing country.

- “Strains” of classical scrapie may be defined according to several criteria: incubation period, brain pathology, clinical manifestations, interspecies transmission capability, and biochemical characteristics (Morales et al, 2007).

- There are two clinically meaningful types of strains of classical scrapie commonly found in the United States. The most frequently identified are valine-independent and valine-dependent strains. The valine-independent strains are those where an arginine (R) at codon 171 confers resistance in sheep. The valine-dependent strains (Evoniuk et al 2005) (where an alanine (A) at codon 136 confers resistance in sheep) are much less frequently found in the United States as evidenced by the low proportion of scrapie cases with the VRQ allele (USDA, 2006).
- However, the scrapie “strains” present in one country appear to differ from those present in another country. For example, the valine-dependent strain is the predominate strain currently circulating in the United Kingdom as evidenced by the high proportion of cases with the VRQ allele (Baylis et al, 2004). Furthermore, there appear to be strains of classical scrapie for which neither A at 136 or R at 171 provide resistance since cases have been reported in sheep of the ARR/ARR and ARR/ARQ genotypes in some countries (Groschup et al, 2007).
- Given the above, international trade in female sheep for breeding based solely on genotype or the importation of sheep and goat protein for use in animal feeding, from an exporting country, zone, or compartment, other than those of negligible risk or that are part of a trading group that is likely to have the same strains due to past trading practices, as proposed in this draft chapter, may result in the introduction and circulation of “novel” strains of classical scrapie for which there is no genetic resistance.

4. Inadequate surveillance requirements to document negligible or controlled risk:

We believe that several of the requirements proposed for scrapie surveillance programs in the draft chapter are inadequate.

The United States recommends the testing of BOTH the obex AND either lymph nodes or tonsils and including animals culled prematurely, rather than solely those “culled-for-age” in the context of surveillance and monitoring programs. Further, the United States recommends that the limit of detection required for surveillance programs to document negligible or controlled disease risk be re-evaluated and that alternative approaches that define scrapie surveillance requirements in a more transparent manner be considered. Finally, the United States proposes that there be a requirement for Member Countries to evaluate the genotype of the scrapie cases that are detected through surveillance.

- Both the scientific literature (Reckzen, et al, 2007) and data collected through the US scrapie surveillance program (unpublished USDA data) demonstrate that surveillance based on testing obex alone is inadequate to detect early subclinical infection and may result in a false negative rate as high as 24%.
- Data collected through the scrapie slaughter surveillance program in the United States suggests that focusing on populations of sheep that are “culled-for-age” in the context of a scrapie surveillance program will fail to detect the majority of subclinical infections. The median age of death for scrapie infected animals is approximately 3.5 years and only approximately 20 percent of sheep with scrapie are expected to live to be more than 4.5 or 5 years (Wineland 1998, Baylis 2004). Further, the proportion of animals testing positive for scrapie in the United States is highest in 3- and 4-year old sheep. (USDA, 2004). Therefore, the United States believes that it is more efficient to target surveillance on those sheep and goats that are culled prematurely as 2, 3- and 4-year olds rather than those “culled-for-age” at the end of their production cycle.
- Using the calculation method described by Cannon and Roe, a sample size of approximately 3000 animals is required to detect scrapie prevalence at 0.1% in an infinitely large population of sheep and goats over 18 months of age with a 95% confidence. Sampling at this level for seven years results in a cumulative ability to detect approximately 0.01 percent prevalence or 1 case per 10,000. Effective targeting criteria will improve the sensitivity of the surveillance system relative to

random sampling, but this level of testing is likely to remain insufficient to initially document negligible scrapie risk, to detect scrapie if it is newly introduced or to effectively control scrapie if present.

- For example, the United States was unable to make significant progress toward scrapie eradication until approximately 3 percent of the expected cull sheep population was tested through slaughter surveillance. Further, to sustain this progress, it was necessary to increase this percentage to approximately 5 percent.
- Another possible alternative would be to develop recommendations for scrapie surveillance that are similar to those described for BSE surveillance in *Appendix 3.8.4* of the *Code*. Specifically, “point” values are assigned to each sample tested based on the presence or absence of defined risk factors for scrapie infection of the sampled animal (e.g., age, clinical presentation). Members would be required to conduct surveillance that results in a defined number of “points” over the 7- year period to document eligibility for the negligible risk category. Once negligible risk status is achieved, the required “points” can be reduced to a maintenance level. This would reduce variability in the interpretation of the requirements for the limit of detection of a surveillance program, and would facilitate evaluation of a surveillance program relative to an objective standard.
- Member countries that have conducted a risk assessment and have had no risk for introduction of classical scrapie for a period of time before surveillance was implemented should be able to compress sampling to 7 years from date of last possible introduction as long as sufficient samples are collected to determine the prevalence at the specified confidence level.
- Since the primary method of control in many countries is the removal of genetically susceptible exposed animals, genotyping of cases detected through surveillance is a critical element that is missing in the draft chapter.

5. **Failure to identify a “maximum allowable prevalence” in order to retain controlled risk status.** For the “controlled risk” status classification to be meaningful, a “maximum allowable prevalence” must be stated. If the prevalence of classical scrapie cases identified through surveillance systems that meet the requirements for controlled risk status, as set forth in the *Code*, exceeds a predetermined limit, the country should *not* be eligible for this classification.

The United States recommends that a “maximum allowable prevalence” be stated for the Controlled Risk Status classification.

6. **Overemphasis on importation and use of bovine meat and bone meal as a route of scrapie transmission:** Given that the draft Chapter is not intended to address risk mitigation for BSE in small ruminants, we believe there is an over-emphasis on this potential route of transmission in the current draft.

The United States recommends that the requirements in this chapter be limited to the inclusion of products from sheep and goats (instead of from all ruminants) in feed or feed ingredients intended for consumption by animals

- The use of products from sheep and goats as feed or feed ingredients for ruminant or non-ruminant animals represent one possible route of transmission (Philippe, et al, 2005) and a source of environmental contamination with the classical scrapie agent. However, this is not the primary route of transmission for the scrapie agent.
- The need for the exclusion of cattle-derived protein or other animal protein to mitigate BSE risk should be based on a country’s BSE risk status and should be addressed in Chapter 2.3.13 of the *Code*.

7. **Overemphasis on scrapie risk posed by rams:** Although rams do not present a significant risk with respect to transmission of the scrapie agent, the current draft includes requirements for the importation of rams that are more restrictive than those for ewes.

The United States recommends that the requirement for rams be revised in light of the available scientific evidence.

- The only known potential risk from direct exposure to rams is from those of the genotype VRQ/VRQ as described in Konold, et al, 2008.

8. **Failure to address potentially exposed sheep and goats that do not currently reside in the flock where a case was identified (i.e., the index flock).** Animals that previously resided in the index flock or in the flock(s) where the case was born or lambed may have been exposed to and infected with the scrapie agent.

The United States recommends that these potentially exposed sheep and goats be treated the same as exposed sheep and goats that currently reside in the index flock during the course of an epidemiological investigation. Further, if these animals are unavailable for testing, we recommend testing of available sheep and goats that were exposed to them.

- In fiscal year 2007, 14 percent of newly identified scrapie-infected flocks in the United States were detected by testing exposed animals that no longer reside in the infected flock at the time of the investigation or by testing other sheep and goats that were exposed to them if the exposed animals were unavailable.

9. **Failure to consider the genotype of the associated case(s) when classifying animals as genetically resistant.** There is no evidence that sheep that are ARR/VRQ are susceptible to scrapie types that affect AxQ/AxQ sheep.

We recommend that ARR/VRQ sheep not be required to be destroyed in cases where the associated positive case(s) are AA at codon 136.

10. **Failure to recognize scrapie risk posed by the importation of semen and/or embryos/oocytes:** The United States believes that it is appropriate to consider the scrapie risk status of the sheep and goat populations of the *exporting country, zone or compartment* and to utilize additional layers to mitigate risks associated with the importation of sheep and/or goat semen and/or embryos/oocytes.

The United States recommends that semen and embryos be removed from the list of commodities that should not require any scrapie-related conditions, and include additional articles in this chapter with scrapie-related conditions required for the importation of both commodities similar to those in *Articles 2.4.8.8 and 2.4.8.9* of the existing *Chapter*.

- The literature is not conclusive on the scrapie transmission risks associated with embryos (Foster, et al., 1992 and 1996; Wang, et al., 2001). Although the use of embryos collected in accordance with IETS guidelines offers significant risk mitigation, we believe it is appropriate to utilize additional layers to mitigate risk such as genotype testing or ante-mortem or post mortem scrapie testing.
- The literature supports classifying semen as low risk with respect to scrapie transmission. However, the limited number of studies and the lack of diversity of

scrapie “strains” evaluated make it appropriate to utilize additional layers to mitigate risk. (Sarradin, et al., 2008; Palmer, 1957)

11. **Use of the term “small ruminant” to describe sheep and goats:** Small ruminant includes camelids, cervids, and some exotic bovids.

We recommend that “sheep and goats” be used throughout the Chapter rather than the term “small ruminant”.

12. **Failure to set realistic case investigation criteria.** It is neither possible nor useful to investigate all sheep and goats showing clinical signs consistent with scrapie.

The United States recommends restricting the reporting requirement to animals at least 18 months of age that demonstrate clinical signs that are highly suspicious for scrapie, and clarifying that only those clinical suspects that are reported to veterinary officials or identified through commercial slaughter channels can be investigated.

- There are many clinical signs that may be “consistent” with a diagnosis of scrapie, but are variable in presence and severity among individual cases. Further, data collected through the scrapie slaughter surveillance program in the United States, suggest that many of these clinical signs (e.g., wool loss without frequent intense rubbing or skin changes, poor body condition) are commonly reported in aged sheep and are not generally predictive of the classical scrapie infection status of the individual animal (unpublished data). As a result, we recommend that those clinical signs known to be highly predictive of classical scrapie -- CNS signs and/or intense rubbing with skin changes -- be used to identify suspect cases that require reporting and investigation.
- Additionally, the long incubation period for classical scrapie makes it unlikely that scrapie-infected animals less than 18 months of age would exhibit overt clinical signs resulting from scrapie infection and the sensitivity of available tests methods is poor in animals in this age category. Setting a minimum age for reporting would prevent unnecessary investigations when the likelihood of scrapie is very low and improve compliance with this requirement.

13. **Failure to address “isolated” cases of scrapie effectively.** In countries that have a history of scrapie infection, it is likely that cases will be found in flocks that do not routinely engage in commerce. Because these cases do not contribute to the transmission of scrapie infection to new flocks/herds, there needs to be a mechanism for addressing these epidemiologically “isolated” cases without making a country “start over” with respect to obtaining negligible risk status.

The United States recommends including language in Article 2.4.8.3 that allows for these epidemiologically “isolated” cases and removing the reference to “cases born more than 9 years ago”.

- This section allows a country to have negligible risk status even after having scrapie if the case was born over 9 years ago. This means a country could remain negligible risk status without making a determination of whether any spread could have occurred simply because the case was over 9 years of age. Also, some countries would only have to wait about 4-6 yrs before being eligible for negligible status after the identification of a case. This is just one or two incubation periods to identify the possibility of spread. Further, the chapter does not recommend tracing, testing and removing susceptible exposed animals or addressing environmental contamination.
- Unlike BSE, classical scrapie infection can occur in adult animals. An infected animal over 9 years of age was most likely infected with scrapie as an adult. If the infected

animal was indigenous and the source cannot be identified, how can the country be sure no additional infection exists?

14. Failure to provide scientific justification for the list of permitted commodities in Item 1 of Article 2.4.8.1.

We recommend that the list be re-evaluated and those items that have not been substantiated as presenting no risk be excluded or those with some risk but where the intended use mitigates the risk the use be specified.

- There is no known human health risk associated with scrapie. As such, if meat and meat products for human consumption are included in this list, sheep and/or goat milk intended for human consumption should also be added to the list of permitted commodities in Item 1 of Article 2.4.8.1.
- In the vast majority of sheep infected with classical scrapie, actual infectivity or PrPres has been identified in most tissues including the lymphoreticular system (tonsils, spleen, lymph nodes), the gastrointestinal tract, brain, and spinal cord (Hadlow et al. 1979; Hadlow et al., 1980; van Kuelen et al., 1996; van Kuelen et al., 1999, Andreoletti et al., 2000; Heggebø et al., 2002; Caplazi et al., 2004). Infectivity and/or PrPres has also been identified in the placenta (see Hourrigan et al., 1979; Onodera et al., 1993; Pattison et al., 1972; Pattison et al., 1974; Race et al., 1998), blood (Hunter et al., 2002; Houston et al. 2008); peripheral nerves (Groschup et al., 1996), muscle (Pattison and Millson, 1962; Andreoletti et al., 2004; Casalone et al., 2005), salivary gland (Hadlow et al., 1980; Vascellari et al., 2007), kidney (Siso et al., 2006), and skin (Thomzig et al., 2007). In addition, recent work has shown milk and/or colostrum from scrapie infected ewes transmitted the disease to 17 of 18 lambs (Konold et al., 2008).
- The data on the risk of low protein tallow made from scrapie infected tissues particularly for use in milk replacer is limited and some epidemiologic studies suggest an association of milk replacer use with scrapie risk. Taylor et al., 1997 examined the inactivation capacity of different rendering system in regards to scrapie. The presence of infectivity was determined by bioassay into mice. From the onset of this study, it was assumed that tallow was not the vehicle for the transmission of TSE. Hence only 2 tallow samples were examined.

15. Failure to recognize scrapie risk posed by the importation of materials destined for the preparation of biologicals: We believe that the proposed requirements for the importation of sheep and/or goat materials destined for the manufacture of biological materials are inadequate.

The United States recommends that these products originate from sheep and goats born and raised in scrapie free countries, as stated in *Article 2.4.8.12* of the existing Code Chapter.

- In the vast majority of sheep infected with classical scrapie, actual infectivity or PrPres has been identified in most tissues including the lymphoreticular system (tonsils, spleen, lymph nodes), the gastrointestinal tract, brain, and spinal cord (Hadlow et al. 1979; Hadlow et al., 1980; van Kuelen et al., 1996; van Kuelen et al., 1999, Andreoletti et al., 2000; Heggebø et al., 2002; Caplazi et al., 2004). Infectivity and/or PrPres has also been identified in the placenta (see Hourrigan et al., 1979; Onodera et al., 1993; Pattison et al., 1972; Pattison et al., 1974; Race et al., 1998), blood (Hunter et al., 2002; Houston et al. 2008); peripheral nerves (Groschup et al., 1996), muscle (Pattison and Millson, 1962; Andreoletti et al., 2004; Casalone et al., 2005), salivary gland (Hadlow et al., 1980; Vascellari et al., 2007), kidney (Siso et al., 2006), and skin

(Thomzig et al., 2007). In addition, recent work has shown milk and/or colostrum from scrapie infected ewes transmitted the disease to 17 of 18 lambs (Konold et al., 2008).

- Although one may be able to make a point that CNS has the highest titers, attempting to differentiate between spleen, tonsils and lymph nodes is not scientifically sound. Unlike BSE, most sections of the GI tract have been found to have both infectivity and PrPres, hence excluding only ileum is also not sound.
- Sourcing tissues from a country with indigenous scrapie especially for use in biologicals for small ruminants without other precautions presents a risk.

16. Requirements for negligible risk establishments that are overly burdensome or inadequate:

The United States recommends that requirements be established that are practical and that result in a high probability of an establishment being free of scrapie.

- The proposal does not require flocks to restart the accreditation process if scrapie is found as long as the genetically susceptible exposed animals are destroyed. Nor does it require that such facilities be disinfected or that genetically susceptible animals not re-enter the facility. Creating a significant risk of a recurrence from environmental contamination going undetected. Furthermore, it does not address handling of acquired animals that are later determined to be scrapie exposed.
- The proposal does not address handling of acquired animals that are later determined to be scrapie exposed.
- As proposed some establishments could become negligible risk without ever testing an animal for scrapie. A minimum number of animals to be sampled should be established.
- By requiring all animals found dead to be sampled makes it impossible for a flock with more than a few animals to comply. Further, it does not provide a reasonable way to address mass casualties. For example one of our enrolled flocks recently lost 600 sheep due to a feed mixing error. For large flocks it should be possible to sample a representative number.
- The proposed requirements over emphasises the risk of rams when the only evidence for possible transmission by rams is for VRQ/VRQ sheep
- Precluding contact of all kinds is unrealistic and unnecessary given that the disease is not highly contagious. For example being in a show ring with other sheep should not cause a loss of status.

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