The EFSA Journal (2005) 220, 1-7. ***Opinion*** **on the assessment of the age limit in cattle for removal of certain specified risk materials (SRM).**

Opinion of the Scientific Panel on Biological Hazards on the assessment of the age limit in cattle for the removal of certain Specified Risk Materials (SRM).

Question N° EFSA-Q-2004-146

Adopted on 28 April 2005

Summary of Opinion

The European Food Safety Authority (EFSA) was invited by the European Commission to review the previous scientific opinions (Scientific Steering Committee, SSC) on the age limit for the removal of certain bovine tissues as specified risk material (SRM) taking into account a report from the referred OIE-consultation group of experts and additional information.
The assessment of the exclusion of certain SRM at a certain age limit is based on available data of ongoing experimental pathogenesis and dose/incubation period studies and on knowledge of the epidemiology of BSE with respect to age at infection and age at detection by clinical and active surveillance.
On the basis of pathogenesis studies results it can be assumed that in CNS the likely detectable PrP^{Sc}, and consequently the likely detectable infectivity appears at about ¾ of the incubation time. Based on the earliest clinical manifestation seen in pathogenesis studies and assuming that the last quarter of the incubation period would be positive for infectivity, the earliest infectivity would have to be assumed at 26 months. However, this would reflect uptake of the BSE agent via the gut only. Other modes of prion uptake, *e.g.* via the oral mucosa and neural spread, cannot be completely excluded and theoretically might significantly shorten the incubation time. However, there are no observational data at present to support this. As for tonsil and intestine, there is no scientific basis to raise the age limit for their removal.
From the analysis of the epidemiological data, it is observed that the average age of BSE positive cases reported in the EU has been increasing from 86 to 108 months over the period 2001-2004, most likely due to effective control measures. It is further observed that the number of BSE cases reported at an age less than 35 months in past years in the EU has been only 4 out of a total number of 6520 BSE cases on a total of close to 41 million animals tested. The minimum age of BSE cases in EU has been 28 and 29 months (2 animals) in 2001, 32 and 34 months in 2002, 36 months in 2003 and 42 months in 2004. The three youngest animals were emergency slaughter, whereas the remainder of BSE cases in young animals (*i.e.* younger then 48 months, table 1) included all target groups.
If the cautious approach of the former SSC is followed and the minimum age is taken as the denominator for the age at which SRM are to be removed, then a cut-off at 30 months would not cover such young animals if assuming ¾ of the incubation period for the appearance of infectivity in CNS. A cut-off at 21 months would cover the last quarter of incubation time of even the single youngest animal observed since the start of the EU surveillance in 2001.

If the BSE cases in very young animals are not taken into account and the mean age at which BSE is detected in the field is taken as the denominator, then a cut-off at 30 months would represent a considerable but not an absolute safety margin with respect to detectable BSE infectivity.
Present BSE surveillance appears to be equally effective in the EU member states.
Nevertheless, there could be important differences between EU Member States according to differences in culling rates and other factors like stage in the epidemic.

Key words: BSE, specified risk materials, cattle, age, epidemiology.

Background

1. Historical background

(a) In its Opinion of 9 December 1997 the Scientific Steering Committee (SSC) suggested a list of specified risk materials (SRM) to be excluded from human and animal consumption on the basis of relative tissue infectivity, species and age. The SSC concluded that the intestine of young animals should be seen as risk as it is the presumed route of infection. However, it was considered extremely unlikely that the central nervous system was detectably infected below the age of 30 months even in cattle exposed to infection as calves. Nevertheless, the exceptional detection of young animals with clinical signs of BSE supported a cautious approach and, therefore, the SSC recommended the removal of various SRM from cattle 12 months of age or older.

This Opinion was revised and updated by SSC opinions on the human exposure risk via food with respect to BSE (10 December 1999), on the oral exposure of humans to the BSE agent (14 April 2000) and on TSE infectivity distribution in ruminant tissues (11 January 2002).

All those opinions led to the management decision to set the age limit for the removal of SRM (excluding intestine and tonsils) at 12 months.

(b) Cattle born after the total feed ban bear a low risk of being infected if the feed ban is properly implemented. This opens the possibility of raising the age limit for the removal of certain SRM from cattle born after a certain date.

(c) Other assessments of the human BSE risk, such as the assessments carried out by Det Norske Veritas (DNV) Consulting on the exposure of the human population to BSE infectivity over the course of the BSE epidemic in Great Britain (2003), assumes exponential growth of infectivity in CNS tissues in cattle. This means that the infectivity is 1000 times lower when 70% of the incubation period has passed compared to the infectivity in the clinical phase of the disease. Halfway through the incubation period the infectivity would be 15000 times lower than in the clinical phase.

(d) In the framework of the OIE-facilitated consultation between EU and USA on the interpretation and implementation of the OIE standard on BSE a group of relevant experts has produced a final report on SRM. In the report its is stated that "results from an ongoing experimental oral exposure study in cattle (VLA) suggest potential minimum ranges of first detection of PrP^d to the end of the incubation period of 27-35 and 28-35 months, providing an average figure of approximately 78% of the way through the incubation period". The group of experts recommends various SRMs (brain, spinal cord, skull, vertebral column, dorsal root ganglia, eyes) to be excluded from cattle 30 months of age or older.

2. Age distribution of BSE cases in the on-going monitoring programme

In 2001, 10 cases of BSE were detected below 48 months of age. Two positive cases were found in animals below 30 months (two emergency slaughtered animals of 28 and 29 months of age). The youngest healthy slaughtered animal found positive in 2001 was 42 months.

In 2002, 7 cases of BSE were detected below 48 months of age. The youngest positive case was found in a 32 months old casualty slaughtered animal in UK. The youngest case in animals born outside UK and Portugal was a 39 months old healthy slaughtered animal born in Denmark and slaughtered in Portugal.

In 2003, 4 BSE cases below 48 months had been reported in the EU15: a 36 months old healthy slaughtered animal in Spain, one 45 months old suspect animal in Germany, one 46 months old dead-on-farm animal in Germany and a 46 months old casualty slaughtered animal in UK. In addition, Slovenia reported a 44 months old dead-on-farm animal and the Czech Republic reported one 36 months old and one 42 months old healthy slaughtered animal.

In 2004, 7 cases below 48 months were detected in the EU25, aged 42 to 47 months. The youngest case (42 months) was a healthy slaughtered animal in Slovakia.

Another observation was that the mean age of the BSE cases in 2003 increased by 6 months compared to 2002 and 17 months compared to 2001.

The number of cases in the ongoing surveillance programme between 49-60 months is listed below:

Number of BSE cases in cattle aged between 49 - 60 months			
BSE cases	**Healthy slaughter**	**Emergency slaughter/fallen stock**	**Suspects/culled animals**
2001	38	50	33
2002	14	40	15
2003	16	14	9
2004	17 + 3*	19 +4*	5

*: BSE cases in new Member States; all other cases were in the EU15

3. Implementation of the feed ban

According to European Commission services (DG SANCO), a progressive improvement of the implementation of the feed ban has been observed since its application on 1 January 2001 but low levels of contaminated feed continue to be reported. In 2002, 31 (0.12%) breaches were detected in more than 26,000 targeted samples in ruminant feed and the levels of contamination were very low. The same tendency is observed on the partial data available for 2003.

Terms of reference

The European Food Safety Authority (EFSA) is invited to give a technical advice on the relevance of the report from the referred OIE-consultation group of experts and, should its conclusions be found relevant, to review the previous scientific opinions on the age limit for

the removal of certain bovine tissues as specified risk material taking into account the OIE report and additional information.

Assessment

The Scientific Panel on Biological Hazards refers to the report of the Working Group in **Annex** for full details on the assessment.

Conclusions:

1.1 The OIE consultation report

The Scientific Panel on Biological Hazards agrees with the relevance of the OIE consultation report for the review of the age limit for SRM removal, with some minor changes. http://www.efsa.eu.int/science/biohaz/biohaz_opinions/opinion_annexes/934_en.html

In the absence of definitive evidence we recommend an approach based on experimental studies and knowledge of the age distribution of BSE affected cattle in the European Union and elsewhere, the Specified Risk Materials (SRM's) to be excluded will have to be assessed in view of the probability of BSE cases at certain age points in the different EU 25 Member States.

1.2 Justification to eventually change the age limit on the basis of the results of pathogenesis studies and epidemiological data.

- On the basis of pathogenesis studies it can be assumed that in Central Nervous System (CNS) the likely detectable PrP^d, and consequently the likely detectable infectivity appears at about ¾ of the incubation time. However, it remains unclear as to the relationship between first detectable PrP^d in the CNS and the incubation period in relation to dose and the age of the animals infected in a natural setting.
- Based on the earliest clinical manifestation seen in pathogenesis studies and assuming that the last quarter of the incubation period would be positive for infectivity, the earliest infectivity would have to be assumed at 26 months. However, this would reflect uptake of the BSE agent via the gut only.
- The average age of BSE positive cases reported in the EU has been increasing from 86 months in 2001 to 108 in 2004.
- The number of BSE cases reported at an age less than 35 months in past years (as from the start in 2001 till end of 2004) in the EU accounted for 0.06 % of all BSE cases reported since 2001.
- The minimum age of BSE cases in EU has been 28 and 29 months (2 animals) in 2001, 32 and 34 months in 2002, 36 months in 2003 and 42 months in 2004.
- If the cautious approach of the former Scientific Steering Committee (SSC) is followed and the minimum age is taken as the denominator for the age at which SRM are to be removed, then a cut-off at 30 months would not cover such young animals if assuming ¾ of the incubation period for the appearance of infectivity in CNS; a cut-

off at 21 months would cover the last quarter of incubation time of even the single youngest animal observed since the start of the EU surveillance in 2001.

- If the BSE cases in very young animals are not taken into account and the mean age at which BSE is detected in the field, is taken as the denominator, then a cut-off at 30 months would represent a considerable but not an absolute safety margin with respect to detectable BSE infectivity.
- However the most appropriate approach would be to conduct back calculation modelling that is depending on data availability from individual countries.
- There may be important differences between EU Member States according *e.g.* to differences in the length of implemented surveillance, in culling rates and other factors like stage in the epidemic.
- There is no scientific basis to raise the age limit for removal of tonsil and intestine.

2 Recommendations

- The main issue that needs to be addressed with respect to options for estimation of the age limit for the removal of SRM is the likelihood of the infectivity in SRM derived from infected cattle at different age groups. Estimation of this likelihood of infectivity would require back calculation modelling with further assessment of experimental and epidemiological data, in particular as indicated in "Approach 4" in the annex.
- Completion of a Quantitative Risk Assessment on SRM including age distribution would be an additional valuable element when assessing the age-related risk of SRM.

DOCUMENTATION PROVIDED TO EFSA

Letter from the European Commission, DG SANCO (D(2004)/JOV/khk/421060) including the mandate and supporting documents.

Relevant SSC opinions:

- Opinion of the Scientific Steering Committee on Listing of specified risk materials: a scheme for assessing relative risks to man. Adopted at its meeting of 9 December 1997.
- Opinion of the Scientific Steering Committee on the Human Exposure Risk (HER) via food with respect to BSE. Adopted at its meeting of 10 December 1999.
- Opinion of the Scientific Steering Committee on Oral exposure of humans to the BSE agent: infective dose and species barrier. Adopted at its meeting of 13-14 April 2000.
- Opinion of the Scientific Steering Committee on TSE infectivity distribution in ruminant tissues (State of knowledge, December 2001). Adopted at its meeting of 10-11 January 2002.
- Update of opinion on TSE infectivity distribution in ruminant tissues, initially adopted by the Scientific Steering Committee at its meeting of 10-11 January 2002 and amended at its meeting of 7-8 November 2002

OIE-facilitated consultation between EU and USA on the interpretation and implementation of the OIE standard on BSE (May 2004). Draft Report on Specified Risk Materials.

Exposure of the human population to BSE infectivity over the course of the BSE epidemic in Great Britain and the impact of changes to the Over Thirty Months Rule" Philip J Comer and Paul J Huntly, DNV Consulting, 2003.

AFSSA-SAISINE n°2003-SA-0334 du 5 Mars 2004. Avis de l'Agence française de sécurité sanitaire des aliments concernant la modification de l'âge minimum des bovins concernés par le retrait de la colonne vertébrale.

EC (2004). EUROPEAN COMMISSION. Report on monitoring and testing of ruminants for the presence of transmissible spongiform encephalopathy (TSE) in the EU in 2003, including the results of the survey of prion protein genotypes in sheep breeds.

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ANNEX

Report of the Working Group (WG) which deals in detail with the assessment:
http://www.efsa.eu.int/science/biohaz/biohaz_opinions/opinion_annexes/933_en.html

The EFSA Journal (2005) 220, 1-21. Annex to the Opinion. Report of the Working Group on the assessment of the age limit in cattle for the removal of certain specified risk materials (SRM).

Annex to the opinion of the Scientific Panel on Biological Hazards on the assessment of the age limit in cattle for the removal of certain Specified Risk Materials (SRM).

Report of the Working Group

1. Assessment

The assessment of the exclusion of certain Specified Risk Materials (SRM) at a certain age limit *e.g.* from cattle 30 months of age or older should be based on data of ongoing experimental pathogenesis and dose/incubation period studies and on knowledge of the epidemiology of Bovine Spongiform Encephalopathy (BSE) with respect to age at infection and age at detection by clinical and active surveillance.

1.1. Experimental studies

Prior to experimental studies of BSE in cattle, knowledge concerning the detection of transmissible spongiform encephalopathy (TSE) infectivity in organs relative to incubation period was confined to studies of scrapie agents in rodent models. The assessment of the occurrence of initial infectivity in the Central Nervous System (CNS) relative to incubation period in cattle is based experimentally on essentially two approaches; one concerns oral exposure and sequential kills to examine the spread of infectivity and/or disease-associated prion protein (PrP^{Sc}) in relation to time (pathogenesis studies) and is described in 1.1.1.1; the other examines the incubation period range relative to dose (attack rate studies) and is described in 1.1.1.2. The statistical approach to estimate the point of first detectable CNS infectivity described in 1.1.1.3 relies on results of both of the former approaches. Observations from the experimental studies have variously included detection of infectivity by bioassay and/or detection of PrP^{Sc} immunohistochemically or biochemically and in studies of BSE in cattle similar sensitivities of detection of infectivity by mouse bioassay and of PrP^{Sc} by a rapid PrP detection method and by immunohistochemistry has been demonstrated (Grassi *et al.*, 2001; Wells *et al.*, 2005). While therefore the relationship between PrP^{Sc} and infectivity is clearly a fundamental issue and one of continuing scientific debate, for practical purposes here the assumption is made that PrP^{Sc} detection is a proxy for infectivity.

1.1.1. Assessment of spread of infectivity and/or PrP^{Sc} in relation to time (pathogenesis studies) and the earliest detectable infectivity in the Central Nervous System of cattle PrP^{Sc}

1.1.1.1. Data from Veterinary Laboratory Agency (VLA, UK) pathogenesis studies in cattle

Before studies of the oral exposure of cattle to the BSE agent were conducted, a range of experimental mouse models of scrapie found that after oral exposure, infectivity was detectable in the CNS at approximately 54% of the incubation period (Kimberlin and Walker, 1988 and 1989) and in the absence of data relevant to cattle, it was assumed that a similar value of 50% might apply to BSE.

Experimental studies of the pathogenesis of BSE at the VLA have been conducted in essentially three phases:

1. The initial oral exposure and sequential kill study (VLA study reference: SE1901/ MO3011) comprised forty Friesian/Holstein calves, assembled from farms in GB with no history of BSE. At four months of age, thirty were each dosed orally with 100g of pooled brain stems from cases of BSE. Ten calves received no treatment and served as controls. Clinical monitoring of cattle was maintained throughout the study. Starting at six months of age (2 months after exposure), and then at four month intervals, until 22 months after exposure, three challenged calves and one control calf were killed. Thereafter challenged and control cattle were killed at discretionary intervals, with the final kill at 40 months after exposure (Wells *et al.,* 1996 and 1998). A large range of tissues, including CNS tissues, were sampled aseptically from each animal killed at each time point for infectivity assays in mice.
2. Selected tissues, including certain CNS tissues, from the above study were further assayed for infectivity by intra-cerebral inoculation of cattle (VLA study reference: SE1824/25/MO3006/7) (Wells *et al.,* 2005).
3. A further oral exposure and sequential kill study (VLA study reference: SE1736) comprising a total of three hundred calves aged 4-6 months. 100 calves were dosed with 100 g of BSE affected brain tissue, 100 were dosed with 1g of BSE affected brain material and 100 were retained as un-dosed controls. Study of the tissues from this is in progress and will extend knowledge of the pathogenesis of BSE by defining PrP^{Sc} detection in nervous system tissues relative to time after exposure by application of rapid test and confirmatory diagnostic technologies. However, the study will not be completed until 2006.

In former SSC opinions (EC, 2002a, b) on the relation of infectivity in relation to incubation period it was concluded that the initial VLA pathogenesis study did not provide interpretable data on the relationship between the earliest detectable infectivity in CNS (or any other tissue) and incubation period after experimental oral infection of cattle with 100g of pooled brain material from clinically BSE affected cattle. In this experimental study, in which the lower limit of the incubation period range was 35 months, evidence of infectivity in the CNS was detected at 32 months, but not at 26 months after dosing (Wells *et al,* 1998). At 32 months post-exposure brainstem and all regions of the spinal cord showed infectivity, whereas no infectivity was detectable within the CNS at 26 months post-exposure. It must be emphasised that these data are limited resulting from one experiment utilising a relatively high dose exposure model with small numbers of recipient animals. Furthermore, the experimental design was not capable of providing estimations of incubation period. It might be inferred, for example, that spread of detectable concentrations of infectivity and PrP^{Sc} throughout most of the CNS has occurred at some time in the 6 month period between 26 and 32 months. However, only one animal was killed at 26 months post-exposure and should this animal not be representative of the mean rate of pathogenetic events at this time, there is the

possibility that spread of infection to the CNS could have been taking place from at least 22 months post-exposure (the preceding kill time point in the study), that is from 10 months prior to demonstrable infection in the CNS. Clearly, generalisations cannot be made from one animal. These results refer to the initial oral exposure pathogenesis study (Wells *et al.* 1998; VLA study reference: SE1901/ MO3011).

Nevertheless, results from the more recent additional experimental oral exposure study in cattle (VLA study reference: SE1736, from which no results are published) in which 100 cattle were dosed with 100 g of BSE affected brain tissue, and 100 cattle were dosed with 1g of BSE affected brain material, are very similar , at least for the higher dose. With the higher dose (100g), disease-associated prion protein (PrP^{Sc}) was detected by immunohistochemistry (IHC) first at 30 months post exposure, histological changes (in one animal) occurred at 33 months and definite clinical disease was first apparent at 35 months. For a 100g dose (with comparable mouse infectivity per g of tissue) the two oral exposure/sequential kill studies suggest potential minimum ranges of first detection of PrP^{Sc} or infectivity to the end of the incubation period of 27-35 and 28-35 months respectively, providing an average figure of approximately 78% of the way through the incubation period. These preliminary observations go some way to suggesting that for the 100g dose group the timing of initially detectable infectivity/PrP^{Sc} in the CNS of cattle with BSE (at least at the level of the medulla) bears a reproducible temporal relationship to the onset of clinical signs.Completed results of the larger study (100 X 100g and 100 X 1g) will not be available until 2006, although, in terms of initial detection of PrP^{Sc} in CNS (medulla only) and of incubation periods (where animals lived to develop clinical disease), there is agreement with the previous study (Wells, personal communication). Data from the 1g dose group gives the earliest detection of PrP^{Sc} and histological changes in the medulla (obex) at 44 months post exposure. Results from the 1 g dose group will be finalised during spring 2006 allowing further comparisons with the 100g dose group. In a worst case assumption, considering a high dose of 100 g and infection at birth, with an earliest experimental incubation time of 35 months in the pathogenesis studies, the CNS of a bovine would be possibly positive as early as at 26 months. However, this incubation period is not representative of the incubation period range of the majority of field cases of BSE as estimated from age specific incidence.

Data from experimental oral exposure studies of pathogenesis do not directly provide interpretable data on the relationship between initial CNS infection and incubation period because, given the sequential kill protocol of the studies, the incubation period range of all animals cannot be determined. It is necessary therefore to utilise also data from studies of the incubation period range relative to dose (attack rate studies).

1.1.1.2. Data from studies of incubation period range relative to dose (attack rate studies).

For modelling of exposure dynamics in the BSE epidemic, the VLA conducted experimental studies to estimate attack rate and dose-response curve for BSE after oral

exposure (VLA Studies SE1918 and SE1930). The study has been carried out in two consecutive phases; the first phase examining the oral dose range 300g, 100g, 10g and 1g and the second phase examining a ten fold reducing dose range of 1g to 1mg. This second experiment replicated the approach used in the first experiment with a range of single exposure doses of 1mg to 1g of the same pooled brainstem homogenate. The second phase of the study is incomplete but data from the first phase, relevant to the doses used in the pathogenesis studies is available but as yet unpublished (BBP1/92).

Oral exposure to a single 100g dose gave a mean incubation of almost 45 months (range 33-61 months). Data for the 1g groups have to date given an incubation period range of 47-75 months (Wells, personal communication). Given the range of incubation periods, observed after different single oral doses of BSE agent in cattle, it is clear that cattle experiments do not provide consistent incubation times as compared with experimental TSE models in rodents. This adds further caution to the interpretation of individual incubation results from the pathogenesis studies.

1.1.1.3. Provisional statistical approach

A preliminary statistical analysis for estimating the point of first detectable infectivity combines the incomplete data on infectivity/PrP^{Sc} detection in the medulla from both cattle oral exposure studies [VLA study references: SE1736 and SE1901/MO3011) and the attack rate (dose response) studies in cattle][1].
A plot of the relationship between the probability of detecting infectivity in the medulla and the number of months before clinical onset is given in Figure 1, along with the upper and lower 95% confidence limits. There is greater than a 99% probability of detection at 3 months immediately prior to the onset of clinical signs (95% CI: 1-6) and less than a 1% probability of detection at 13 months prior to onset of clinical signs (95% CI: 8-18).

[1] It is assumed that the probability of detectable infectivity in CNS tissue depends on the number of months before clinical onset. This means that the probability of detecting infectivity at a given kill time will depend on the incubation period in the animal from which the tissue was taken, *i.e.* the number of months before clinical onset equals the incubation period minus the kill time. Using estimates of the incubation period from the attack rate studies (providing incubation period relative to dose), the data on detectable infectivity is converted from the number of months post-inoculation to the number of months before clinical onset. Taking also the probability of infection given the dose into account, logistic regression is used to estimate the relationship between the probability of detectable infectivity/PrP^{Sc} and the number of months before clinical onset. The output is the probability of detectable infectivity/PrP^{Sc} given the number of months before onset for the CNS tissue data analyzed. The outcome will not be absolute but the modelling of the involvement of nervous system tissues relative to incubation will specify confidence limits. Interim results based upon IHC observations on medulla from an incomplete range of animals in the SE 1901/ MO3011 and SE1736 studies provide an illustration of the approach that will ultimately be based on observations from a range of CNS sites, using several PrP^{Sc} detection methods. It must be stressed that these incomplete observations are confined to a single method applied to a single location in the CNS.

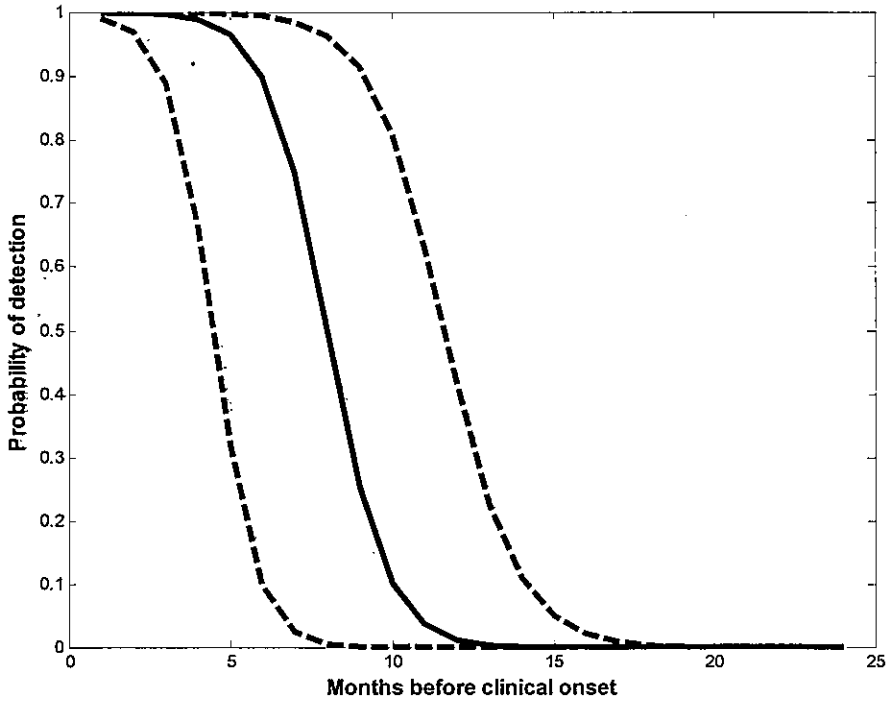

Figure 1: the maximum-likelihood estimate of the relationship between the probability of detection and the number of months before clinical onset, along with upper and lower 95% confidence intervals.

The application of the analysis to naturally occurring BSE for estimation of the optimum age for removal of CNS and associated SRM tissues is interdependent on epidemiological data on age specific incidence, modelling of likely ages of maximum exposure and the evolution of the epidemic relative to control measures.

1.1.2. Experimental data from mouse and hamster models of pathogenesis involving infection in the oral cavity

Assessment of the earliest possible BSE infectivity of the CNS has to take into account other potential routes of infection than uptake via the gut. Such other routes are indicated in a few experimental approaches to be possibly neurogenic via the oral cavity such as the buccal, gingival mucosa, dental pulpa or tongue (Carp, 1982; Frigg *et al.*, 1999; Ingrosso *et al.*, 1999; Race *et al.*, 2000; Bartz *et al.*, 2003).
Carp (1982) and Smith *et al.* (2003) used a mouse model with the scrapie strain 139A. In the study group the incisal gingival area was superficially scarified with sterile forceps and scissors. In addition, some mice had one or both upper incisors removed. This was followed by the application of brain homogenate (0.03 mL) from scrapie-infected mice to the gingivae of the 26 study mice and a group of 24 non-scarified control mice. Of the

non-scarified mice, 71% became infected compared with all of the scarified mice, the latter also demonstrating a shorter incubation period.
Bartz *et al.* (2003) demonstrated that the transmission of the agent of transmissible mink encephalopathy (TME) is about 100.000 fold more efficient by inoculation of PrP^{Sc} into the tongue of hamsters than by oral ingestion. Initial appearance of TME in the brain stem was found in the hypoglossal nucleus at 2 weeks post infection. The incubation time was reduced from 191 day after oral ingestion (1 out of five animals affected) to 79 +/- 5 days (16 out of 16 animals affected). It is conceivable that PrP^{Sc} might be injected through the oral tissues during the uptake and chewing of feed, especially in young individuals, where frequency of defects of the oral mucosa is considerably increased due to dentition. Direct infections via the oral cavity would also present an explanation for the finding of positive BSE test results in unexpectedly young bovines *i.e.* younger than 24 months.

In view of these findings it has to be taken into account that the infection of the CNS might also, theoretically, occur in bovines considerably earlier as suggested from the pathogenesis studies where such routes of infection were not taken into account.
It has to be noted that these experimental rodent models included surgical intervention as the essential feature of the approach to involving cranial nerves in pathogenesis and therefore, although rapid neuro-invasion through the oral cavity is conceivable and can be shown in some experimental animal models, caution must be expressed as to the feasibility of such events occurring in the course of natural infection with the BSE agent. Furthermore, there are no similar experimental data for ruminants. Finally, considering the extensive experience with various aspects of the BSE epidemic such cases of possible rapid neural invasion would have been expected to be recognised if they had occurred.

1.1.3. Infectivity in tonsil and intestine.

Since the last Scientific Steering Committee opinion (EC, 2002b) new data on the tonsil alone became available: a detailed study of experimental BSE pathogenesis (Wells *et al.*, (2005) demonstrated traces of infectivity in the palatine tonsil of cattle killed ten months after exposure. Thus, there is no scientific basis to raise the age limit for removal of tonsil and intestine.

1.1.4. Conclusion on pathogenesis studies

On the basis of the VLA pathogenesis studies results (100g and preliminary results 1g) it can be assumed that in CNS the likely detectable PrP^{Sc}, and consequently the likely detectable infectivity appears at about ¾ of the incubation time. This is somewhat deviating from the former SSC opinions where an average figure of approximately 50% of the way through the incubation period was assumed. However, full results of the 1g dose group are pending and will not be available before spring 2006, but it is not expected that these will show a shorter incubation period as with the 100g dose group.

Based on the earliest clinical manifestation seen in the VLA pathogenesis study and assuming that the last quarter of the incubation period would be positive for infectivity, the earliest infectivity would have to be assumed at 26 months. However, this would reflect uptake of the BSE agent via the gut only. Other modes of prion uptake, *e.g.* via the oral mucosa and neural spread, cannot be completely excluded and theoretically might significantly shorten the incubation time. However, there are no observational data at present to support this.
As for tonsil and intestine, there is no scientific basis to raise the age limit for their removal.

1.2. Epidemiological data.

1.2.1. Age dependent susceptibility at infection

Evidence from epidemiological analyses of BSE in dairy herds in GB indicates that cattle are most at risk in the first six months of life (Arnold and Wilesmith, 2004). Studies of the French BSE epidemic indicate that most infections occur between 6 and 12 months of age (Supervie and Costagliola, 2004). Given these epidemiological findings, it is assumed that most infections occur in the first year of life.

1.2.2. Age distribution of BSE cases in the EU

In 2001, a total of 11 cases of BSE were detected below 48 months of age (see table 1). From these cases only two positive cases were found in animals below 30 months (two emergency slaughtered animals of 28 and 29 months of age). The youngest healthy slaughtered animal found positive in 2001 was 42 months.
In 2002, 7 cases of BSE were detected below 48 months of age. The youngest positive case was found in a 32 months old casualty slaughtered animal in UK[2]. The youngest case in animals born outside UK and Portugal was a 39-month old healthy slaughtered animal, born in Denmark and slaughtered in Portugal.
In 2003, 4 BSE cases below 48 months had been reported in the EU15: a 36 months old healthy slaughtered animal in Spain, one 45 months old suspect animal in Germany, one 46 months old dead-on-farm animal in Germany and a 46 months old casualty slaughtered animal in UK. In addition, Slovenia reported a 44 months old dead-on-farm animal and the Czech Republic reported one 36 months old and one 42 months old healthy slaughtered animal.
In 2004, 7 cases below 48 months were detected in the EU25, aged 42 to 47 months. The youngest case (42 months) was a healthy slaughtered animal in Slovakia.

[2] It is noted that in the UK in the OTM (Over Thirty Months) animals (healthy slaughter population in other MS) less than 42 months of age have not been subject to the active surveillance until November 2004. Therefore in the UK younger animals (< 42 months) will only be detected in the clinical suspect, fallen stock and casualty surveillance streams.

Table 1. Cases reported by Member States (MS), detected by active and passive surveillance and found positive for BSE in animals younger than 48 months since the start of the surveillance in 2001 till 2004.

Year	Total cases	Country	Date of Birth	Age (months)	Target Group
2001	11	DEUTSCHLAND	14/09/1998	28	Emergency Slaugther
		DEUTSCHLAND	17/08/1998	29	Emergency Slaugther
		DANMARK	23/05/1998	42	Healthy slaughtered
		FRANCE	18/08/1997	42	Healthy slaughtered
		ESPAÑA	30/12/1997	43	Emergency Slaugther
		ESPAÑA	20/07/1997	43	Emergency Slaugther
		DEUTSCHLAND	10/09/1997	44	Fallen Stock
		ESPAÑA	31/10/1997	45	Healthy slaughtered
		UK	25/08/1996	46	Suspect
		UK	16/02/1998	46	Emergency Slaugther
		ESPAÑA	27/08/1997	47	Fallen Stock
2002	7	UK	25/05/1999	32	Emergency Slaugther
		PORTUGAL	1/08/1999	34	Healthy slaughtered
		PORTUGAL	1/03/1999	39	Healthy slaughtered
		ESPAÑA	5/07/1999	41	Fallen Stock
		IRELAND	1/02/1999	45	BSE eradication
		IRELAND	1/02/1999	46	Suspect
		DANMARK	8/12/1998	47	Fallen Stock
2003	7	ESPAÑA	11/12/2000	36	Healthy slaughtered
		CZECH REPUBLIC	15/04/2000	42	Healthy slaughtered
		SLOVENIA	12/07/1999	44	Fallen Stock
		DEUTSCHLAND	24/12/1999	45	Suspect
		DEUTSCHLAND	24/12/1999	46	Fallen Stock
		CZECH REPUBLIC	15/01/2000	46	Healthy slaughtered
		UK	12/03/1999	46	Emergency Slaugther
2004	7	SLOVAKIA	1/02/2001	42	Healthy slaughtered
		SLOVAKIA	1/01/2001	44	Healthy slaughtered
		ESPAÑA	11/05/2000	44	Fallen Stock
		DEUTSCHLAND	14/06/2000	46	Healthy slaughtered
		DEUTSCHLAND	16/06/2000	46	Fallen Stock
		ESPAÑA	13/12/2000	47	Healthy slaughtered
		PORTUGAL	26/04/2000	47	Healthy slaughtered

The number of BSE cases in cattle in the ongoing EU surveillance programme, aged between 49-60 months are listed below in Table 2.

Table 2. Number of BSE cases in cattle in the EU between 49-60 months of age.

Number of BSE cases in cattle between 49-60 months of age			
Year	**Healthy slaughter**	**Emergency slaughter/fallen stock**	**Suspects / culled animals**
2001	38	50	28
2002	14	40	10
2003	18	18	10
2004	17 + 3*	19 + 4*	5

* Cases in new MSs; all other cases were in the EU15

The figures presented in Table 3 and Table 4 illustrates the risk potential for the presence of infected CNS in the different age populations for 2002 and 2003. It can be seen that the number of cases occurring at an age less than 35 months is low and consequently the associated relative risk is minimal.

Table 3. Cases of BSE according to age range in the European Union in 2002 (EU 15, except Austria)

Age (mo)	Total tested	Percent	Cases	Rate per million	Relative risk
≤35	3,365,907	33	2	0.6	1
> 35	6,830,078	67	2,124	309.5	500
Total	**10,195,985**	**100**	**2,126**		
≤ 59	5,539,944	54	66	11.9	1
> 59	4,656,041	46	2,060	440.2	37
Total	**10,195,985**	**100**	**2,126**		

Table 4. Cases of BSE according to age range in the European Union 2003 (except Austria)

Age (mo)	Total tested	Percent	Cases	Rate per million	Relative risk
≤ 35	2,370,015	24	0	0	NA
> 35	7,457,241	76	1,364	182.9	NA
Total	**9,827,256**	**100**	**1,364**		
≤ 59	4,008,820	41	44	11.0	1
> 59	5,818,436	59	1,320	226,9	21
Total	**9,827,256**	**100**	**1,364**		

Another observation was that the mean age of the BSE cases in 2003 increased by 6 months compared to 2002 and 17 months compared to 2001. The average age of reported BSE positive cases in the years 2001 to 2004 (EU 15) was 86 months for 2001; 97 months for 2002; 103 months for 2003; and 108 months for 2004 (EU 25) (EC 2004), most likely due to effective control measures. Thus, the risk (assuming no new exposures) of occurrence of animals with infected CNS by 30 months of age, has decreased.

1.2.3. Age distribution of young BSE cases outside the EU.

In Japan, Yamakawa *et al.*, reported in 2003 two cases of BSE in Holstein steers respectively 21 and 23 months of age, as a result of the screening of approximately 2.5 million cattle of all ages from October 18, 2001 till September 30, 2003. Since the start of the comprehensive testing in Japan in 2001, 14 BSE cases were confirmed (by 7 December 2004): 3 in 2001, 2 in 2002, 4 in 2003 and 5 in 2004. However, it is unclear whether the two very young cases were adequately identified and formally confirmed. Moreover, they seem to be epidemiologically peculiar as their cohort would have been expected to yield further cases.

1.2.4. Probability for the presence of BSE infected cattle with an age under 30 months covering the EU-25

To evaluate the probability for the presence of BSE infected cattle with an age under 30 months covering the EU-25, the starting point was to try to assess the probabilities starting from age 40 months down, if possible in a month-wise table, but at least with data for ages of 40, 32, 24 and 16 months. If enough data were available, probabilities on a country wise basis could also be made.

The question, in summary, is whether there is sufficient evidence to recommend the raise the age limit for the removal of SRM from cattle. Essentially this is a difficult question to answer directly. This is simply because the risk of infection for the birth cohorts of interest, as indicated above, remains unknown. Insufficient time has elapsed, given the incubation period distribution, for infection to be detected by the current screening/diagnostic methods. Although within the EU15 the ultimate ban on the use of MMBM came into effect in January 2001, it would be presumptuous, based on past experience, to assume that this ban was fully effective in preventing new infections. The safest assumption is therefore that the infection status of the birth cohorts of current interest remains unknown, and there is some likelihood that they carry a low prevalence of infected animals. In epidemiological terms this requires examining the probability of the presence of BSE infected cattle at various cut-off ages.

1.2.5. Possible epidemiological approaches

There are different options that may be considered in addressing this issue. Most of these options will depend on the availability of reliable data as well as the assumptions and the background related to these sets of data. Further details on data sets essential for this task and on various approaches and options are given in the ANNEX to this report.

One option is to analyze the results of surveillance to determine the youngest animals found positive in the affected cohorts. This approach is only possible for the EU15, as the full surveillance programme has not been in operation long enough in the EU10 to make sensible epidemiological use of the data.

Another approach, to assess the risks presented from an older cut off point *e.g.* at 30 months, is to conduct back-calculation modelling as has been the case in the review of the OTM Scheme in the UK (Ferguson and Donnelly, 2003). This was followed by the risk analysis conducted by Comer and Huntly (2003). The back calculation approach requires some assumptions to be agreed and made, especially on the effectiveness of the control measures introduced (in the EU15) in January 2001. This does have the advantage that it introduces some transparency in the modelling and obviously a range of assumptions can be made with respect to the prevalence of infection in the birth cohorts of interest.

There are potential difficulties in this approach. The main one relates to data availability of the age structure of the cattle population and the survival of the individual birth cohorts in individual countries.
There is also perhaps a resource problem in conducting such analyses for individual MS, but given appropriate demographic data relevant models are available which could be used, perhaps with minor modifications.
Those EU MS's that have had a later start of active surveillance (EU 10) might consider adopting this analytical approach when 12 months full surveillance data become available.
If the modelling approach were to be adopted it follows that some time would elapse before the results would be available. This is not entirely a disadvantage as it would be helpful if the envisaged analysis of the data relating to the Great Britain pathogenesis study and the attack rate studies currently in progress were more complete. This is dependent on further testing of tissues that is in progress or firmly planned.

1.2.6. Discussion

In order to have an epidemiological basis for a change in the age limit for SRM removal it is appropriate to adopt the suggested modelling approach followed by the application of a risk analysis. The latter could be as described by Comer and Huntly (2003) and modified in the light of the analyses at the VLA.

There appear to be two issues to be considered in adopting this approach. The first is how the modelling is to be conducted and by whom and how it could be overseen. An Expert Group could be constituted to agree assumptions and examine results. The second issue is whether the results from the analyses of the individual MS in the EU can be aggregated to allow a single change across the MS.

1.2.7. Conclusions on epidemiological data

The number of BSE cases reported at an age less than 35 months in past years (as from the start in 2001 till end of 2004) in the EU has been only 4 out of a total number of 6520 BSE cases on a total of close to 41 million animals tested. The minimum age of BSE cases in EU has been 28 and 29 months (2 animals) in 2001, 32 and 34 months in 2002, 36 months in 2003 and 42 months in 2004. However, young animals below 35 months of age accounted only for 0.06 % of all BSE cases reported since 2001. The three youngest animals were emergency slaughter, whereas the remainder of BSE cases in young animals (*i.e.* younger then 48 months, table 1) included all target groups.
The average age of BSE positive cases reported in the EU has been increasing (86 months in 2001; 97 in 2002; 103 in 2003; 108 in 2004 (EU 25)), most likely due to effective control measures.

If the cautious approach of the former SSC is followed and the minimum age is taken as the denominator for the age at which SRM are to be removed, then a cut-off at 30 months

would not cover such young animals if assuming ¾ of the incubation period for the appearance of infectivity in CNS; a cut-off at 21 months would cover the last quarter of incubation time of even the single youngest animal observed since the start of the EU surveillance in 2001.
If the BSE cases in very young animals are not taken into account and the mean age at which BSE is detected in the field is taken as the denominator, then a cut-off at 30 months would represent a considerable but not an absolute safety margin with respect to detectable BSE infectivity.
However the most appropriate approach would be to conduct back calculation modelling that is depending on data availability from individual countries.

Present BSE surveillance appears to be equally effective in the EU MS. Nevertheless, there could be important differences between EU MS according to differences in culling rates and other factors like stage in the epidemic.

2. Conclusions

2.1. The OIE consultation report

The Scientific Panel on Biological Hazards agrees with the relevance of the OIE consultation report for the review of the age limit for SRM removal, with some minor changes.
http://www.efsa.eu.int/science/biohaz/biohaz_opinions/opinion_annexes/934_en.html

In the absence of definitive evidence we recommend an approach based on experimental studies and knowledge of the age distribution of BSE affected cattle in the European Union and elsewhere, the Specified Risk Materials (SRM) to be excluded will have to be assessed in view of the probability of BSE cases at certain age points in the different EU 25 MS.

2.2. Justification to eventually change the age limit on the basis of the results of pathogenesis studies and epidemiological data.

- On the basis of pathogenesis studies it can be assumed that in Central Nervous System (CNS) the likely detectable PrP^{Sc}, and consequently the likely detectable infectivity appears at about ¾ of the incubation time. However, it remains unclear as to the relationship between first detectable PrP^{Sc} in the CNS and the incubation period in relation to dose and the age of the animals infected in a natural setting.
- Based on the earliest clinical manifestation seen in pathogenesis studies and assuming that the last quarter of the incubation period would be positive for infectivity, the earliest infectivity would have to be assumed at 26 months. However, this would reflect uptake of the BSE agent via the gut only.

- The average age of BSE positive cases reported in the EU has been increasing from 86 months in 2001 to 108 in 2004.
- The number of BSE cases reported at an age less than 35 months in past years (as from the start in 2001 till end of 2004) in the EU accounted for 0.06 % of all BSE cases reported since 2001.
- The number of BSE cases reported at an age less than 35 months in past years (as from the start in 2001 till end of 2004) in the EU accounted for 0.06 % of all BSE cases reported since 2001.
- If the cautious approach of the former Scientific Steering Committee (SSC) is followed and the minimum age is taken as the denominator for the age at which SRM are to be removed, then a cut-off at 30 months would not cover such young animals if assuming ¾ of the incubation period for the appearance of infectivity in CNS; a cut-off at 21 months would cover the last quarter of incubation time of even the single youngest animal observed since the start of the EU surveillance in 2001.
- If the BSE cases in very young animals are not taken into account and the mean age at which BSE is detected in the field, is taken as the denominator, then a cut-off at 30 months would represent a considerable but not an absolute safety margin with respect to detectable BSE infectivity.
- However the most appropriate approach would be to conduct back calculation modelling that is depending on data availability from individual countries.
- There may be important differences between EU MS according *e.g.* to differences in the length of implemented surveillance, in culling rates and other factors like stage in the epidemic.
- There is no scientific basis to raise the age limit for removal of tonsil and intestine.

3. Recommendations

- The main issue that needs to be addressed with respect to options for estimation of the age limit for the removal of Specified Risk Materials (SRM) is the likelihood of the infectivity in SRM derived from infected cattle at different age groups. Estimation of this likelihood of infectivity would require back calculation modelling with further assessment of experimental and epidemiological data, in particular as indicated in "Approach 4" in the annex.
- Completion of a Quantitative Risk Assessment on SRM including age distribution would be an additional valuable element when assessing the age-related risk of SRM.

4. Acknowledgements

The Chairman, rapporteur and members of the working group are acknowledged for their valuable contribution to this mandate. The members of the working group are:

 *The EFSA Journal (2005) 220, 1-21. Annex to the Opinion. Report of the Working Group* **on the assessment of the age limit in cattle for the removal of certain specified risk materials (SRM).**

Paul Brown, Herbert Budka (Chairman), James Hope, Hans Kretzschmar, Ernst Lücker Mo Salman, Emmanuel Vanopdenbosch (Rapporteur), Gerald Wells and John Wilesmith.

5. Documentation provided to EFSA

Letter from the European Commission, DG SANCO (D(2004)/JOV/khk/421060) including the mandate and supporting documents.

Relevant SSC opinions:

- Opinion of the Scientific Steering Committee on Listing of specified risk materials: a scheme for assessing relative risks to man. Adopted at its meeting of 9 December 1997.
- Opinion of the Scientific Steering Committee on the Human Exposure Risk (HER) via food with respect to BSE. Adopted at its meeting of 10 December 1999.
- Opinion of the Scientific Steering Committee on Oral exposure of humans to the BSE agent: infective dose and species barrier. Adopted at its meeting of 13-14 April 2000.
- Opinion of the Scientific Steering Committee on TSE infectivity distribution in ruminant tissues (State of knowledge, December 2001). Adopted at its meeting of 10-11 January 2002.
- Update of opinion on TSE infectivity distribution in ruminant tissues, initially adopted by the Scientific Steering Committee at its meeting of 10-11 January 2002 and amended at its meeting of 7-8 November 2002

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ANNEX: DATA THAT ARE ESSENTIAL FOR ESTIMATION OF THE AGE LIMIT FOR REMOVAL OF SRM AND VARIOUS APPROACHES AND OPTIONS.

Essential data sets:

The most essential data sets that are needed are:

1. The age distribution of cattle that are slaughtered in a country or all EU.
2. The age distribution of cattle that are tested in a country or all EU. Test results should be also available.
3. The time period for the above two distributions given the fact that such distributions are different for the last few years as compared to the late 1990s.
4. Sensitivity and specificity of the screening and confirmatory tests.
5. Estimation of incubation periods from the pathogenesis data that can be used to derive a distribution.

Most of the above sets of data can be obtained from the existing surveillance programs within selected EU MS or the entire union.

Various age classes can be explored but they should have practical use in terms of their application. The following age classes should be considered: 40, 32, 24 and 16 months, and of course, data for these classes should be available.

Other data sets such as cattle population distribution in the country by age group, geographical location, and beef versus dairy purpose can be helpful but they are not necessary. One may argue that age distribution of live cattle is necessary to predict the proportion of cattle that are missed for testing. However, it is considered that the proportion of slaughtered cattle by various age distributions is a better reflection of the actual eligible infected animals that can spread the disease agent. Therefore, the distribution of the live cattle population is not directly relevant for this task.

Approaches/options:

1. Calculation of the likelihood of getting an infected animal (positive test) for selected age classes. The likelihood then can be compared with other age classes to determine the relative magnitude of the risk for a specific group. Either Relative Risk or Population Attributable Risk can be used for this determination. Confidence intervals for these estimates can be derived to reflect the variations.

   Requirements:

   - Surveillance data in terms of the number of animals tested stratified by age group and the testing results are needed.

Advantage:

- Calculation is easy to perform using existing surveillance data.
- Outcome/result is straightforward and it is understandable.

Limitations:

- It is a crude approach to determine the risk for specific age group mainly to bias in the collection of the surveillance data which reflect the rules instead of the proportion of the slaughtered animals.
- The age classes for estimation of the risk are limited by the available data and therefore not all the desired age classes can be assessed.
- The proportion of the slaughtered animals in each age class may not be equally distributed to the proportion of the tested animals. Therefore, a standardization of these proportions may be required.

2. Determine the age of the youngest animals found positive in the affected cohorts using the existing surveillance system among EU MS with reliable data.

Requirements:

- Standardized slaughtered surveillance data are essential so that merging into one data set can make be intelligible.
- The assumption is that the past decline in the risk of infection in successive cohorts will be sustained.

Advantage:

- This is a simple approach and may lead to some relaxation of the age limit for SRM removal.

Limitations:

- It is crude and could not be defended with any significant scientific rigor.

3. Determine the age of the youngest animals found positive using the experiments from UK

Requirements:

- The existing experiment data with a detailed description of the IHC results and the affected organs.
- The assumption is that the detection of the agent in a specific organ is associated with the infectious status.

Advantage:

- It is a simple approach and acceptable to basic scientists.

Limitations:

- The sample size is limited and is the most conservative estimation of measuring the age limit.
- The natural route of infection is different from some of the experimental inoculations using the intra-cerebral route.
- The dose used in these experiments is relatively high which may lead to overestimation of the risk.

4. Estimation of the risk for each using a conventional epidemiological/risk assessment process. The process will include estimation of the risk for each age group using both observational and experimental data. The process can be either deterministic (point estimates) or stochastic (distribution) for the input/output.

Requirements:

- Specific assumptions in terms of incubation period, infectivity, and population dynamic.
- Surveillance and experimental data to initiate selected inputs.
- Risk assessment modeling either in qualitative or quantitative types.
- Expertise in conducting risk assessment modeling with consideration as to input from experts.

Advantage:

- Precise risk estimates for each age group that can be quantitative with the potential to obtain distributions that can be used in the risk management decision process.
- Science-based approach to determine the relative magnitude of the risk excluding zero risk.

Limitations:

- Model assumptions are critical and require substantial planning as well as inputs from various experts and specialists. Consensus will be difficult if not impossible. Data acquisition for this model represents a serious technical problem.
- The risk assessment modeling is a dynamic process and once begun will be never-ending. The users therefore, could get frustrated.
- Output from the model can be interpreted differently by some users. Some interpretations may be erroneous. Therefore, team involvement is important in the interpretation and writing of the final outcome.

The effectiveness of the control measures introduced during the period of the data used for this calculation is not considered. Thus, there is a potential for biased estimations of the risk.

European Food Safety Authority

SCIENTIFIC PANEL ON BIOLOGICAL HAZARDS

Technical Advice
On "OIE-facilitated consultation between EU and USA on the interpretation and implementation of the OIE standard on BSE (May 2004)"

Question N° EFSA-Q-2004-146

The European Food Safety Authority (EFSA) was invited by the European Commission (EC) to give a technical advice on the relevance of the report from the referred OIE-consultation group of experts and, should its conclusions be found relevant, to review the previous scientific opinions on the age limit for the removal of certain bovine tissues as specified risk material taking into account the OIE report and additional information.

Conclusion:

The Scientific Panel on Biological Hazards agrees with the relevance of the OIE consultation report for the review of the age limit for SRM removal, with some minor changes and without, at this stage, expressing an opinion on the proposal to change the current age limit.

Question 1

Assuming a common scientific understanding of the pathogenesis of BSE, at what time during the incubation period are various SRMs (brain, spinal cord, skull, vertebral column, dorsal root ganglia, eyes) considered to become infective?

Response 1

- There is no conclusive evidence to enable us to define the precise time, relative to the incubation period or age of clinical manifestation, at which the central nervous tissue becomes infected.
- In as much as the size of the cattle to human species barrier is unknown, it follows that we cannot determine the time at which central nervous tissues become infectious for humans.
- For these reasons the previous precautionary approach to SRM removal of CNS and associated tissues has been based on approximately half of the age of the youngest cases recorded; where age is used as a surrogate for incubation period.
- A range of experimental and observational data provide information on which to formulate a revised approach.

Question 2

What influence do the outcomes of an effective BSE surveillance programme and appropriate risk management measures have on the recommended age of removal of these SRMs? Can this influence be quantified?

Response 2

- The purpose of BSE surveillance is to determine the presence of the disease and, if occurrence of BSE is demonstrated, to estimate the prevalence and monitor the evolution of the epidemic and thus the efficacy of feed bans.
- Scenarios where effective surveillance could influence SRM measures are conceivable in relation to:
  - Epidemics of high incidence where the volume of data is sufficient to demonstrate that the age structure of cases is significantly different (i.e. younger) from that observed in other high incidence countries. In such instances, removal of CNS SRMs might be considered ***necessary at any appropriate young age.*** In such a circumstance, the relative effect of such a change could, theoretically, be quantified.
  - Circumstances in which surveillance data, over time, are deemed to have shown confidence limits of prevalence consistent with freedom from BSE. In such a case, the removal of SRMs might cease to be a requirement altogether.
- In the course of a surveillance programme, it may become possible to review aspects of SRM removal.

Recommendation:

The Scientific Panel on Biological Hazards recommends:

In the absence of definitive evidence we recommend an approach based on experimental studies and knowledge of the age distribution of BSE affected cattle in the European Union. ***This will have to be assessed in view of the probability of BSE cases at certain age points in the different EU 25 Member States.***

The WG and the panel will now consider further work on the second part of the mandate, analyzing further experimental and epidemiological evidence to consider a possible review of the age limit at which SRM should be removed.

Scientific Panel members:

Herbert Budka, Sava Buncic, Pierre Colin, John D Collins, Christian Ducrot, James Hope, Mac Johnston, Günter Klein, Hilde Kruse, Ernst Lücker, Simone Magnino, Riitta Liisa Maijala, Antonio Martínez López, Christophe Nguyen-The, Birgit Noerrung, Servé Notermans, George-John E Nychas, Maurice Pensaert, Terence Roberts, Ivar Vågsholm, Emmanuel Vanopdenbosch.