Opinions adopted by the Scientific Steering Committee at its meeting of 19-20 February 1998

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*** Note:**

Preliminary opinions are open for comments until 16 March 1998, 24h00. They will be finalised at the next meeting of the Scientific Steering Committee (26-27 March 1998). They should be addressed to:

For matters related to specified risk materials, geographical aspects of BSE, criteria to evaluate the TSE status, etc.:	joachim.kreysa@dg24.cec.be
For matters related to gelatine, tallow and meat and bone meal, etc.:	paul.vossen@dg24.cec.be

Preliminary opinion on BSE risk

Adopted by the Scientific Steering Committee
At its plenary meeting of 19-20 February 1998

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Preliminary opinion on BSE risk

Adopted by the Scientific Steering Committee At its plenary meeting of 19-20 February 1998

In considering the risk of BSE, the SSC recognised three major issues:

1. the risk of human exposure arising from the direct consumption of potentially infective material;
2. the risk to man from ingesting or being exposed to processed potentially infective material (e.g. tallow or gelatine), and
3. the risk of propagating the infection by recycling the infective material through animal feed (MBM).

A key factor in considering these three risks is the relative infectivity of tissues in an infected bovine. By excluding the most infective tissues from the processing chains the risk of transmitting BSE can be considerably reduced. This position is confirmed by recent information which allows to quantify the contribution of the different most infective tissues to the overall infective load of an infected bovine (see table 1).

Table 1: Relative infectivity of suggested specified risk material from an infected bovine (data provided by SEAC, February 1998)

Tissue	**Infectivity density ($CoID_{50}/g$)[1]**	**Weight (kg) per Animal of 537 kg**	**ID_{50} per animal**	**% of total infective load per animal**
Brain	10	0.5	5000	64.0
Spinal cord	10	0.2	2000	25.6
Trigeminal ganglia	10	0.02	200	2.6
Dorsal root ganglia	10	0.03	300	3.8
Ileum	$3.2*10^{-2}$	0.8	256	3.3
Vertebral column	$3.2*10^{-3}$	5.0	16	0.2
Spleen	$3.2*10^{-3}$	0.8	3	0.04
Eyes & rest of head	$3.2*10^{-3}$	11.6	37	0.5

[1] Cattle oral Infectious Dose 50%

The SSC confirmed its SRM listing of 9/12/97 on the basis of infectivity but noted that with suitable slaughtering procedures in place the lungs are not contaminated and therefore may be excluded from that list. Similarly the SSC is satisfied that practical procedures in the slaughterhouse can be defined to ensure that the ileum is separated from other parts of the intestine. If these procedures are ensured then only the illeum need be considered infective.

As concerns the importance of the species of the animals, the SSC re-affirmed its conclusions that the risk of BSE in sheep and goats can not be estimated, although no cases of TSE, caused by the BSE agent, have been detected in small ruminants, outside experiments. It therefore reaffirms its conclusion of 9/12/97 that the heads and spinal cords of sheep and goats should be removed from animals aged one year or more and the ileum and spleen should be discarded at all ages. However, in order to confirm this conclusion, a risk assessment should be carried out addressing the probability of BSE being present in sheep and goats. This requires information which currently is not available to the SSC.

1. Human exposure by direct consumption

With regard to Human exposure by direct consumption the SSC recognised that a listing of SRMs should take account of their specific infectivity and the total weight of different tissues (see table 1).

Based on the quantitative data, the SSC recognised that the brain, spinal cord, dorsal root ganglia and trigeminal ganglia constitute the major hazards for direct human consumption. These would constitute 96% of the infective load from an infected animal, entering the food chain in the last nine months before the clinical manifestation of the disease (youngest animal ever seen: 20 month*)*. The age of the animal therefore affects the risk of infectivity, too. So the SSC reaffirms its view of 9/12/97 that SRMs should be removed from animals over 12 months of age in countries which are not BSE free or don't have a negligible risk.

Mechanically recovered meat may also be a risk material since it contains dorsal root ganglia.

2. Human exposure via processed products (tallow and gelatine)

Concerning the risk carried by Tallow and Gelatine the SSC endorsed the opinions prepared by its working groups (see annexes B and C). It underlines that these opinions are based on a risk assessment aiming at achieving the lowest possible risk. It will complement them with a quantitative risk assessment, as soon as the necessary information becomes available.

3. Propagation of the disease via the feed chain

Concerning the risk carried by MBM the SSC endorsed the opinions prepared by its working group (see annex D). It underlines that this opinion is based on a risk assessment aiming at achieving the lowest possible risk. It will complement them with a quantitative risk assessment as soon as the necessary information becomes available.

4. Sourcing of animals

The geographical source of the animals has been considered in great detail at three different levels:

- the risk that an infective animal enters the food chain (incident risk);
- the risk that an infective animal would propagate the disease by entering the feed chain (propagation risk), and
- the risk to humans of being exposed to an infective dose of BSE (human exposure risk).

On examining the dossiers it became clear that the currently available data are not sufficient to confidently classify these countries. In order to obtain the necessary information the SSC endorses the list of the desirable data presented in Annex A.

At this stage the SSC can not provide a definitive view on geographical categories. It will return to this issue and will also devise a methodology to asses information provided by countries in this respect.

Annex A to the SSC Opinion of 19-20 February 1998

Opinion on the contents of a "complete dossier of the epidemiological status with respect to TSEs"

Based on the list of factors contributing to the incident and propagation risks in a geographical area as established by the SSC in its opinion of 23/1/98

Adopted by the Scientific Steering Committee at its plenary meeting of 19-20 February 1998.

Annex A to the SSC Opinion of 19-20 February 1998

Opinion on the contents of a "complete dossier of the epidemiological status with respect to TSEs"

Based on the list of factors contributing to the incident and propagation risks in a geographical area as established by the SSC in its opinion of 23/1/98

Adopted by the Scientific Steering Committee at its plenary meeting of 19-20 February 1998.

Foreword

The incident risk of today is determined by the propagation risk 3 to 8 years ago. This is depending of the rendering system and the MBM feeding to cattle at that time, and influenced by the potential imports of infected animals and infective MBM even before that. It is therefore of utmost importance to receive complete historical data, at least for the critical factors.

In all cases information should cover statistical, legal and control aspects. It is also essential that all data be sufficiently well documented. The data available to the inspection services of the Commission will be used as complementary source of information.

The SSC wishes to stress that the following is an ideal set of information and accordingly does not expect that any country or area will be in a position to provide all such data. However, the more information available, the more precise the risk assessment. An effort will be made to interpolate missing data, but in certain cases worst case assumptions will have to be used to replace not available data.

1. Structure and dynamics of the cattle, sheep and goat populations

The picture of the cattle, sheep and goat populations in the geographical area under consideration needs to be as complete as possible. Population data should therefore include information on the:

- absolute numbers of animals per species, alive and at time of slaughter. Although absolute numbers do not affect the propagation risk, they are necessary in the case of an outbreak to determine the time required for the infection to disappear;
- age distributions of animals per species (and if possible also by sex and type, i.e. dairy/beef) and age distributions at time of slaughter;
- geographical distribution of the animals by species and breeds. This is only considered important if the infection rate from sheep to cattle is significant;
- geographical distribution of the animals by husbandry systems, herd sizes and production purposes. This information is useful to provide cross checks on MBM[1] usage and age distribution of animals.
- system of identification, and capacities for tracing of animals: the identification of the movement of animals between farms, herds and geographical areas.

[1] Meat and bone meal, assumed to be the major rout of transmission for BSE.

These data should be provided on an annual basis and ideally for the period from 1980 (at least from 1988) onwards in order to understand their dynamics.

2. Animal trade

The import of infected animals is a major source of risk for an infected animal entering the food and feed chain. A comprehensive picture of the relevant trade flows was therefore felt to be essential and data, ideally from 1980 (minimum requirement: 1985 to 1990) onwards (annual basis, global figures are not sufficient), are requested. These should include information on:

- import and export of cattle, sheep and goats with special emphasis on population data on these animals as mentioned under 1 and a clear definition of the geographical origin of the animals;
- trade within the geographical area, with special emphasis on population data on these animals as mentioned under section 1 and with a clear definition of the geographical origin of the animals;
- imports of embryos of cattle, sheep and goats into the geographical area and a clear definition of the geographical origin of the embryos;
- imports of semen of cattle, sheep and goats into the geographical area and a clear definition of the geographical origin of the semen;
- use made of imported animals (fattening, breeding, milk production, .., this information should for each of the different uses indicate the age distribution at slaughter);
- use made of imported embryos or semen;
- mechanisms used by slaughterhouses to identify animals and their origins, as well as data from these procedures.

3. Animal feed

The consumption of infectious MBM must be seen as (one of) the major source(s) of BSE. It is therefore essential to have a good understanding of the consumption and source of MBM in a given geographical area for assessing the probability that BSE might occur (in future) in its animal populations (incident risk).

With regard to the quantity of MBM used, the information should include a full profile on data, ideally from 1980 (minimum: 1985 to data of MBM-ban introduction) onwards. The data have to be provided on an annual basis and should be relating to:

- the production of domestically produced MBM and its usage per species and husbandry system (in particularly the fraction of MBM fed to cattle, alternatively the amount of composite fed given to the different types of cattle at different age);
- imported MBM (country of origin) and its usage per species and husbandry system (in particularly the fraction of that MBM fed to cattle, alternatively the amount of composite fed given to the different types of cattle at different age);.
- exported MBM

4. Meat and bone meal (MBM) bans

The existence or not of an MBM-ban and its effective implementation will strongly influence the risk that BSE is or has been transmitted by this route. Data on the MBM-ban should therefore include data about the:

- nature of the bans (full description of details, including species involved);
- dates of introduction;

- actual implementation, policing and compliance/breaches figures (annual basis since date of introduction);
- possibilities of cross-contamination with other feed (to this end the use of MBM for other species has to be quantified. Further information on this is requested under point 7)

5. Specified bovine offal (SBO) and specified risk materials (SRM) bans

The suppression of SBOs and SRMs from entering the food and feed chains will reduce the risk of BSE infection further. Data are therefore requested on this issue. (It is obvious that details can not be provided if no SBO or SRM-ban was in force.) These should include data about the:

- nature of the bans (full description of details, such as species, tissues and ages of materials used);
- dates of introduction;
- Actual implementation, policing and compliance/breaches figures (annual basis).

6. Surveillance of TSE, with particular reference to BSE and scrapie

The quality of these data is very important for the estimation of the basic risk that an infective (with or without clinical signs) animal could enter the food and feed chain (incident risk). Information is therefore requested on the surveillance system for BSE and SCRAPIE (the latter because of the possible link between scrapie and BSE and vice versa). This information should include data preferably from 1985 onwards, on the following:

- incidence of laboratory confirmed cases of BSE and scrapie (per year);
- kinetics of age distribution, geographical distribution, and countries of origin of cases;
- incidence of neurological disorders in which TSE could not be excluded on clinical grounds in different animal species;
- methodologies and programs of surveillance and recording of clinical cases of BSE and scrapie, including training for awareness of farmers, veterinarians, control services and authorities;
- incentives for reporting cases, e.g. compensation and rewarding schemes;
- methodologies of laboratory confirmation and recording of suspect cases of BSE and scrapie;
- strains of BSE and scrapie agents possibly involved;
- existing systems or current plans for targeted active surveillance.

7. Rendering and feed processing

The quality of the MBM in terms of its capacity to transmit BSE is influenced by the process conditions under which it is produced. Information on the rendering and feed-processing systems in the given geographical region is therefore requested.

This information should include data, ideally from 1980 (minimum: 1985 until implementation of MBM ban) onwards, as far as possible on an annual basis and about the:

- description of all rendering and feed processing systems used (information on an annual basis) and description of the nature of the records of all the rendering and processing plants (e.g. feed mills) involved; (reports of the inspection services of the Commission shall be used to verify the implementation);

- quantitative and qualitative parameters of MBM and tallow production by each of the processing systems and by each plant (i.e. the data should allow to calculate the amount of different raw materials rendered by the various processes per year over the target period, particularly 1985 to 1995; alternatively the fraction of material rendered per type of process would be appropriate), the geographical areas from which the rendered materials originate (annual basis) and the type of material used (of particular interest is the amount of brain and spinal cord material which is entering the rendering system as well as the treatment of any SRM, fallen stock etc.);
- parameters on separate processing lines for materials from healthy and suspected animals (annual basis);
- transport and storage systems for MBM or MBM containing feed which ensure the prevention of cross contamination of MBM-free feed (particularly important after the date of the MBM-ban implementation, indication of any change by data and nature of the change).

8. BSE and scrapie related culling

The culling of BSE and scrapie cases and of related animals will strongly influence the dynamics of the disease. For countries which have not had any case (neither native nor imported), this information will allow to assess the potential impact of such an event. Information should be provided about:

- targets of culling with detailed specification of criteria (if appropriate including the evolution of these targets and criteria over time since 1985 onwards);
- time of introduction (and of any change since its first introduction);
- animals involved (annual basis since first introduction, animal population characteristics as specified under 1, including imported animals);
- sizes of herds involved.

Note:

Countries should provide data as far as possible in tabular form and prepare their dossiers in line with the structure given above.

Annex B to the SSC Opinion of 19-20 February 1998

THE SAFETY OF GELATINE

Report and preliminary scientific opinion adopted at the Scientific Steering Committee meeting of 19-20 February 1998

Definition

For the purpose of the present opinion, gelatine is defined as a mixture of polypeptides obtained by partial hydrolysis of the collagen contained in bones and skins from bovines and/or pigs after successive treatments: degreasing, acid treatment, alkaline treatment (liming), washing, filtration, ion exchange, sterilisation and oxidising treatment.

2. Introductory note (Stryer, 1981)

Collagen is a family of fibrous proteins having a very high tensile strength found in connective tissues such as the organic matrix of bones, hides and skins, tendons, cartilage, the cornea of the eye, blood vessels and teeth.

The structural unit of collagen is tropocollagen. This protein is formed of three helical units wrapped around one another with a right handed twist. Each of these helices contains about 1000 aminoacids. The amino-acid sequence of collagen is highly distinctive; nearly every third residue is glycine (35%). Other important aminoacids are alanine (11%), proline (12%), aside the unusual hydroxyproline (9%) and a few % of hydroxylysine.

The triple stranded helical rod is about 3000 Å long and 15 Å in diameter. The structure is stabilised by hydrogen and other bonds, changing with the age of the animal.

When a solution of collagen is heated in water, the viscosity is abruptly decreased, the helical structure denatured and disorganised with the production of gelatine.

3. Background

The Scientific Steering Committee was requested to advise the Commission on the risk exposure of humans and animals to BSE from gelatine and its co-product dicalcium-phosphate. For humans special attention should be focused on the use of gelatine in the food chain, pharmaceuticals and cosmetics including parenteral use.

As stated in the opinion of 9 April 1996 of the Scientific Veterinary Committee, there are three major factors which influence the risk of exposure from animal by-products in relation to BSE:

(1) The titre of infectivity likely to be found in the tissue used in its manufacture.

(2) The effectiveness of the process used for the inactivation (or the elimination) of the agent.

(3) The route of application (e.g. food, cosmetics and medicinal products).

The Scientific Veterinary Committee stressed also "that the full data on all gelatine manufacturing processes have not been published, hence a full risk analysis cannot be carried for gelatine." By-products, such as gelatine, aminoacids and dicalciumphosphate were recognised as giving the best possible guarantees of safety if produced in a process which ensures that all material is subjected to degreasing, followed by acid and/or alkaline treatment followed by heating to 120° and these up to 140°C for 4 seconds. The product should be labelled to show the process to which it has been subjected. The Scientific Veterinary Committee emphasised also that: "*the specified bovine offals from UK cattle (brain, spinal cord, thymus, spleen, intestine and tonsils) as well as vertebral column and any tissues resulting from trimming carried out in accordance with EC and UK legislation on BSE, should not be used for*

any purpose (food, feed, medical, pharmaceutical or cosmetic use), whatever the process to which they are subjected."

A similar assessment should also be carried out for material originating from other countries with native cases of BSE.

The preceding opinion differs largely from the 1992 and 1994 opinions expressed by the Scientific Veterinary Committee in 1992, stating that "whatever the tissue source, there is a negligible risk from trading in gelatine for technical use, for consumption or in cosmetics additional guarantees are therefore not necessary.

In its opinion of 15 April 1996 on Products derived from bovine tissues, especially gelatine, tallow and di-calcium-phosphate in relation with Bovine Spongiform Encephalopathy, the Scientific Committee Food concluded*: "Based upon current incomplete knowledge regarding BSE and its possible transmission to humans and the uncertainty about the inactivation of the infective agent, the Committee at present is only able to advise that bovine source materials for these products are to be taken only from geographical areas where BSE does not occur in epidemic conditions. The Committee urges that data required for a scientifically based risk assessment be generated by relevant bodies. Further research is needed especially to develop specific, sensitive and rapid methods for detection of the causative agent in biological materials."*

At its meeting of 16 April, 1996, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (E.M.E.A.) endorsed the following conclusion on the potential risk of gelatine in relation to Bovine Spongiform Encephalopathy (BSE): "Three cumulative factors contribute to the safety of gelatine used in pharmaceuticals:

- Manufacturers of gelatine used for pharmaceutical use should not use tissues derived from bovine animals, slaughtered in the UK .
- The additive effects of washing, acid decalcification followed by acid and prolonged alkaline treatment, filtration and sterilisation are sufficient to eliminate any possible risk.
- Source tissues used in the manufacture of gelatine are classified as having no detectable infectivity.

On the 3rd of April, 1997, the Scientific Steering Committee / Multidisciplinary Scientific Committee (SSC/MDSC) expressed a similar opinion ato that of the Scientific veterinary Committee on 9 April, 1996, stressing especially: "That at the moment no production method can be considered as safe for gelatine and related products if the base material used is potentially infectious." The opinion further states: "The control of the nature, the geographical origin and the quality of the starting material is currently the only means to assure the protection of public health. The control applied to the starting materials must be subjected to intensive monitoring." The SSC/MDSC also confirms its view that *"the following tissues should not be used as starting materials: skull, vertebral column, brain, spinal cord, eye, tonsil, thymus, intestine and spleen. (SEE Commission decision of 11th June, 1996, 96/362/EC). The Committee urgently recommends to establish an effective system for the monitoring and the surveillance of TSE's. (especially BSE and scrapie)."*

In its Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products **(**Revised draft 14 - rev.1 of 2nd

September 1997), the C.P.M.P. concludes that the risk of transmission of infectious agents can be greatly reduced, by controlling a number of parameters which include:
- the source of the animals (including on the basis of their age);
- the nature of animal tissue used;
- the production and transformation processes,

The European Commission Decision N° 97/534/EC of 30 July 1997 confirms the conditions for the manufacture of gelatine from bone raw material. In the 15 E.U. member states as well as for third countries exportingto E.U. (the general rule applies to all: both for human consumption and for pharmaceutical and cosmetic use), the following risk materials should be excluded: skull, brain, eye, spinal cord, tonsils. The decision also excludes the use of mechanically recovered meat for human consumption.

So far, bones, a raw material for the production of gelatine, have been considered as a material with no detectable infectivity. Bovine bone marrow, by analogy with bone marrow from sheep with scrapie, was classified as belonging to the category of low potential infectivity materials. In its opinion adopted on 8-9 December 1997, the Scientific Steering Committee states:

> *(on) **dorsal root ganglia**. New (unpublished) evidence shows that the dorsal root ganglia - located within the general structure of the vertebral column - should be considered as having an infectivity for BSE equivalent to that of the spinal cord. The dorsal root ganglia proved infective at the same time after infection as the spinal cord, i.e. 32 months. The trigeminal ganglia were also infective, but so far no autonomic nervous system tissue has been found to be infective. The dorsal root ganglia cannot be removed without extreme difficulty. This therefore means that as a precautionary proposal the removal of the whole vertebral column (other than the coccyx) is now appropriate. Care needs to be taken to ensure that the removal of the vertebral column incorporates the lateral aspect of the vertebral bodies. This dissection may sometimes be difficult in practice unless the musculature is selectively removed from the vertebral bones for selling as bone-free meat.*
>
> *(on) **Bone marrow** :*
>
> 1. *Early studies with mice intracerebrally injected with bone marrow from cattle with spontaneous clinical BSE has not demonstrated infectivity (SEAC, 1994). However, studies on calves, experimentally infected by feeding 100g of BSE infected brain tissue, have now shown bone marrow infectivity in cattle studied at 38 months after feeding the BSE infected brain. These animals were clinically affected by BSE. (MAFF, unpublished evidence 3.12.1997). This has wide-ranging implications because it implies that long bones as well as vertebral columns must be considered potentially infective. The concerns on contamination and the dorsal ganglia mean that on these grounds alone the vertebral columns of older animals should be included in the category of specified risk material.*
> 2. *Several issues now emerge from the new report on bone marrow infectivity. First the apparent infectivity of bone marrow might need to be redefined. Bone marrow (on the basis of scrapie studies) was placed in Category III, i.e. as showing low infectivity. In previous bone marrow*

studies on clinical cases of BSE infected cattle, no infectivity was detected which might have suggested that the WHO classification was inappropriate in persisting with a Category III, rather than a Category IV, rating, i.e. no demonstrable infectivity. However, new evidence shows 2 of 18 mice developing late clinical disease after having been injected with marrow from cattle of 38 months post infection. Another 3 mice also show immuno cytological evidence of the presence of PrP^{Sc}, having been injected with the same bone marrow extract. Given the late development of this demonstrable infectivity in cattle bone marrow despite the substantial infective dose (100 g untreated BSE infective brain) it now seems appropriate to maintain the WHO classification for BSE as well as for scrapie. This signifies thatBSE is increasingly being revealed as having a tissue based infectivity which seems similar to that of scrapie.

3. *This conclusion reinforces the concepts [...]. that the different levels of infectivity do reflect a graded phenomenon and that it is unwise to consider the BSE agent as either present or absent in particular tissues.*
4. *The bone marrow findings also raise the issue of whether bones from older animals, e.g. >30 months, should be removed from the human food chain."*

As far as infectivity of bone marrow is concerned, the working group on gelatine of the Scientific Steering Committee noted that the above statements referred to infectivity resulting from a single group of experimentally challenged cattle. However, no infectivity of the bone marrow of naturally infected bovines has been detected so far, nor of naturally scrapie infected sheep and goats.

4. Non exhausting list of relevant scientific and technical material.

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Dormont, D., 1997b. Letter of 17 February 1998 to the Scientific Steering Committee secretariat, regarding the safety of gelatine. (Original French version only).

E.C. (European Commission), 1994. Report on detailed procedures for the validation of rendering processes adopted by the Scientific Veterinary Committee (Animal health Section) on 12 December 1994.

E.C. (European Commission), 1996. Scientific opinions issued by the Scientific Veterinary Committee on 9.04.96, 26.04.96 and 21.10.96 on Specified risk materials and on the safety of meat and bone meal and of tallow**. (Document N° MDSC/DGXXIV/97/91.)**

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E.F.P.I.A. (European Federation of Pharmaceutical Industries Associations), 1998b. Preliminary Joint Position Paper of the associations of the German pharmaceutical industry (BPI, BAH, VAP and VFA) on the Opinion of 9 December of the Scientific Steering Committee "Listing of specific risk materials: A scheme for assessing relative risks to man". Attached to a letter of 26.01.98 addressed to the Cabinet of Commissioner E.Bonino.

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5. On the production of gelatine

In order to express an opinion on the safety of gelatine it is important to take into account a number of aspects of the gelatine production methodologies and conditions.

5.1 The production of gelatine (see G.M.E., 1997$_{a,b,c}$; 1998)

Gelatin production includes 3 main processes and 3 types of raw material: an acid process for bovine bones, hides and pig skins, an alkaline process for bovine bones and hides and a heat/pressure process for bones. Pig skins are normally submitted to an acid treatment. Starting from bovine raw materials there are at least five alternatives:

a) bovine hides and skin lime alkaline treatment
b) bovine hides and skin soda alkaline treatment
c) bovine bone lime alkaline treatment
d) bovine bone acid treatment
e) bovine hides and skin enzymatic treatment.

5.1.1 The alkaline process

The gelatine manufacturing process includes first a degreasing step of fine crushed bones in hot water (80° to 85°C). Regularly shaking removes a high percentage of proteins. The dried bone chips are then submitted over a total period of 4-5 days, to a sequence of solutions with an increasing hydrochloric acid concentration. The highest concentration being 4% of HCl during 2 days. This demineralisation of the fine bone chips produces a phosphoric liquor that after treatment with lime, will give a precipitate of bicalcium phosphate. (see further). The osseine obtained is washed a further two times with water.

The next step is the liming step. During 45 days the washed osseine is treated with a solution of saturated lime. ($Ca(OH)_2$ = 12.5).

During the extraction step that follows, the limed osseine is treated, under stirring, with sulphuric acid until the pH remains below 6. After frequent water washing, the limed osseine is then 4 times extracted with warm water (>50°C). Each extraction is continued until the obtained gelatine concentration is between 3% and 8%.

The filtration is done in 2 steps. The first with diatomaceous earth, and the second with a cellulose filter. After the filtration step the extract is ion exchanged in sequence over a cation resin and an anion resin. To avoid gel forming a precise temperature is maintained during the filtration and ion exchanged steps.

The gelatine solution is further concentrated by vacuum evaporation to approximately 20%.

With appropriate techniques, the concentrated solutions are sterilised during 4 seconds at 140°C and subsequently cooled.

Finally the concentrated solution is cooled to jellify and after being cut into small pieces, dried for 3 hours in stream of warm air. Careful quality controls are performed on each step in the production chain.

Bovine hides are also treated by alkaline process. According to US-FDA (1997) can safe gelatine be produced from bovine hides from any country, provided that the processors ensure that the bovine hides have not been contaminated with brain, spinal

cord or ocular tissues of cattle residing in - or originating from BSE countries and if they exclude hides from cattle that have signs of neurological disease

5.1.2 The acid process

Bovine bones may also be treated by an acid process. Pig skins are normally submitted to an acid treatment. The liming step is then replaced by an acid pre-treatment where the osseine is soaked overnight at pH below 4.

5.1.3 The heat/pressure process

In stead of applying an acid or alkaline treatment after degreasing, the bones are submitted to a heat/pressure process of 133°C during 20 minutes at 3 bars, followed by filtering. The gelatine obtained is of limited quality and use.

6. Some considerations regarding the safety of gelatine

Regarding the safety of gelatine, the Scientific Steering Committee noted the following:

6.1 The opinion of the association Gelatine Manufacturers of Europe (G.M.E.) on the quality and the sourcing of raw material

The total amount of raw material transformed yearly into gelatine in Europe is estimated to be near 500.000 tons with 100.000 ton gelatine: 52% from pig skins, 21% from bovine bones and 27% from bovine hides. The world-wide production of gelatine is 220.000 tons from which 44% is produced in Europe.

Raw material for one given plant may originate from several sources and may be a mixture of materials from different slaughterhouses and suppliers. Various parts of the production process itself may be spread over several locations. The number of critical points[2] in the whole production chain from source to final product which need to be controlled to minimise or neutralise the risk of possible residual infectivity of the final product, is large and their monitoring may not always be easy and evident.

According to the association Gelatine Manufactures of Europe (G.M.E.), which represents most of the E.U.'s gelatine producers, all of their associated gelatine-manufacturing sites in the European Union are certified according to ISO 9000 international standards. The G.M.E.'s gelatine manufacturers claim to respect the following O.I.E. sanitary guarantees: no sourcing from countries with high BSE infectivity (UK); sourcing only from countries with low infectivity or BSE free. Bones and skins are collected from the meat industry controlled by the official veterinarians' services; they come from animals recognised as suitable for human consumption. For each gelatine lot (even from outside E.U. countries) full documentation allows manufacturers to trace the raw materials "origin" from their reception in gelatine plants. Upstream, bovine bones are subject to a similar traceability in the degreasing plants.

However, given the complexity and multitude of critical points in the overall production process, and given the fact that they are not limited to the conditions within the factory, the SSC is of the opinion that respecting ISO 9000 standards is probably not a sufficient guarantee of the safety of the end product, but that the

[2] In terms of possible hazards in terms of risk for remaining BSE infectivity in the final product

respect of HACCP[3] procedures should be guaranteed and documented. Some of these points are (non exhaustive list): traceability, the source of the raw materials which may be multi-country and multi-supplier, whether or not specified risk materials have been removed, the physical conditions of the various production processes which may be carried out at several places, separate labelling and/or storage of the material according to the intended final use of the gelatine, etc.

6.2 Scientific opinions from the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) and from the FAO-WHO.

Since 1991 the CPMP (part of the EMEA since 1995) emphasises three principles to minimise the risk of transmission of BSE which are scientifically sound: selective sourcing, tissue of origin and safety of the extraction process. For what concerns medicinal products, the CPMP indicated the following conditions for the safety of gelatine (EMEA, 1996):

- raw material from the UK to be excluded
- the source tissues are to be classified as having no detectable infectivity
- the additive effects of washing, acid decalcification, followed by acid and prolonged alkaline treatment, filtration and sterilisation are considered to be sufficient to eliminate risk.

The EMEA opinion concludes that, provided that it is well established that the starting material for pharmaceutical use (active ingredients or excipients) is safe regarding the BSE risk, on the basis of the various measures proposed in the EU guidelines and documented in the application dossier, the finished product is also safe.

In its revised draft of 2 September 1997 of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (EMEA, 1997), the CPMP states that "*For gelatine manufacture, risk from central nervous tissue attached to skulls or vertebrae can be reduced by excluding these bones from the source material.*"

The FAO-WHO granted gelatine the status of foodstuff if it has been processed according to good manufacturing practices. (NMRS report 48 TRS 462-XIV/12). The last opinion of the WHO (27/03/97) was in the same line as their previous opinion: "*The new information does not change previous recommendations regarding milk and gelatine safety in relation of the BSE transmission.*"

6.3 The U.S. FDA's opinion and proposal

The opinion from the FDA is based on the preliminary data presented in 1994 by the gelatine industry in relation to the BSE transmission routes and excludes gelatine as part of its recommendations concerning other bovine ingredients in U.S. FDA regulated products (Federal register of Aug. 29, '94; 55FR.44584) from countries that have reported BSE.

As new information became available suggesting that BSE may be transmissible to humans and because of updated data from the study on the effect of gelatine processing on infectivity, the U.S. FDA decided in 1996 to review its previous guidance on the use of gelatine.

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3 HACCP: Hazard Analysis Critical Control Points

On April 23-24th, 1997 the FDA stressed that the current scientific evidence did not justify the continued exemption of gelatine from restrictions recommended by FDA for other bovine derived material from BSE countries. Based on this review, the FDA decided in September 1997 upon the following recommendations concerning the acceptability of gelatine for use in FDA-regulated products intended for human use:

1. In order to ensure that all parties in the distribution chain take appropriate responsibility, importers, manufacturers and suppliers should determine the tissue species and country source of all materials to be used in processing gelatine for human use.
2. Gelatine produced from bones and hides obtained from cattle residing or originating from countries reporting BSE or from countries that do not meet the latest BSE standards of the O.I.E., should not be used either in injectable, ophthalmic or implanted FDA regulated products or in their manufacture.
3. Gelatine can be used for oral consumption and cosmetics when the gelatine is produced from bones coming from BSE free herds in BSE countries and if SRM's (WHO list) are removed. (heads, spines and spinal cords) or if the bones come from countries BSE free, but fail to meet O.I.E. standards and with removal of heads, spine, spinal cord.
4. Gelatine can be produced from bovine hides from any country, provided that the processors ensure that the bovine hides have not been contaminated with brain, spinal cord or ocular tissues of cattle residing in - or originating from BSE countries and if they exclude hides from cattle that have signs of neurological disease.
5. At this time bovine bones and hides from the US and/or from BSE free countries may be used for gelatine production, provided that they meet the O.I.E. standards.
6. At this time porcine skins from any source country, may be used for gelatine production for human use. Cross-contamination with bovine materials originating from BSE countries or from countries that do not meet the O.I.E. standards are to be avoided and certified.

Thus it seems clear for the U.S. FDA that the potential risk of BSE transmission from bovine bone derived gelatine, varies depending on the country of origin, the raw material, the type of tissue used, the gelatine process used and the route of administration or exposure. Finally it is noteworthy that gelatine-a poor source of protein- and other bovine-derived products from BSE countries intended for animal use are banned by the USDA/APHIS (United States Department of Agriculture / Animal and Plant Health Inspection Service) in the US.

6.4 Other sources of information on the safety of gelatine

6.4.1 Opinion of the pharmaceutical industry.

The pharmaceutical industry believes that provided certain conditions are complied with, removal of SRM's from the production chains is not necessary to ensure the safety of gelatine vis a vis risks of BSE transmission. This is based on the following arguments:

- Advice from scientific expert bodies. (see 6.2)
- Present traceability and sourcing practices for gelatine production.

- The nature of the current standard processing conditions (see 5)

Traceability and sourcing of the raw material seems more important than the nature of the processing conditions.

The European Federation of Pharmaceutical Industries Associations (EFPIA, 1997, 1998) claim to use gelatine only from countries with no or very low BSE disease incidence, or where SRMs are already eliminated from the production process. In addition, it is claimed that each batch of gelatine supplied to the pharmaceutical industry is accompanied by a veterinary certificate which certifies that only healthy animals (fit for human consumption) have been used in the source material, indicates the countries of origin and ensures rigorous traceability.

According to the European Federation of Pharmaceutical Industries Associations the relevant CPMP guidelines have been followed at least since 1991. These guidelines (see above) advocate a combination of careful control of source material and processing conditions. *[EFPIA recommends that the safety of products should be analysed on a case-by-case basis and that the pharmaceutical industry should assess risk and validate the end product]*

The Scientific Steering Committee considers that many pharmaceutical products (including drugs, vaccines, ophthalmic and biotechnology based products as well as injectables are produced using bovine components in their manufacturing process as starting materials, processing ingredients and excipients in final formulations. Pharmaceuticals however are administered with the purpose of conveying benefit and the risk assessment should more appropriately be a risk benefit assessment for individual products, balancing the benefit conferred against the risks identified. The SSC notes that several research institutes are developing and validating methods for assessing risk of BSE in pharmaceutical products, but that a standardised and generally accepted method is still not available. Many of these rely upon the control of source selection of tissues and processing, which remain the best means of minimising risk to patients.

6.4.2. Results from Manzke et al. (1996)

In the production process it is interesting to note that German researchers (Manzke et al., 1996) have shown that during the degreasing step 98-99% of the protein of nervous origin (e.g. S100[4], GFAP[5] and others) are removed. The method used (Elisa test) was very sensitive with a detection threshold from 30 picogr. For S100 and 7 picogr. for GFAP.

The likelihood that animal bones in continental Europe are contaminated with nervous tissue from animals suffering from BSE was previously estimated to be at most 0.0005 (weight) % (Schrieber and Seybold, 1993). It was also noted that total protein from bones before degreasing was 12.9 g/kg and was reduced to 2.4 g/kg after degreasing. (=82% reduction). After the succeeding step in gelatine manufacture, the acid treatment of degreased bones (HCl 4%) during 4-5 days, specific nerve proteins were no longer detectable.

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4 S100 is a nervous protein, soluble in 100% saturated ammonium sulphate.

5 GFAP stays for glial fibrillary acid protein.

In an other experiment, finely crushed bovine heads were used which implies extremely high contamination with brain tissue. Since 1 September 1997, heads as such are no longer used in routine gelatine manufacture. The results obtained confirm those obtained with crushed bone chips: a reduction of specific nerve tissue proteins by 98-99% after degreasing, additionally, total protein content is reduced from 31.8 g/kg to 3.7 g/kg (88%) and no specific nerve proteins were detectable after the acid treatment step using degreased heads.

The authors conclude that "*there is hardly any reason to assume that prions would not be removed similarly as nervous proteins.*"

The Scientific Steering Committee comments that TSE infectivity is not limited to nervous (brain) proteins but is also present in the lympho-reticular system of sheep but not so far in BSE infected bovines, even after spleen and lymph nodes were infected intercerebrally into cattle. The SSC also notes that the above conclusion may be valid for the reduction in protein levels, but not necessarily for infectivity.

6.4.3. Gelatine manufacturers validation studies.

With respect to the possible BSE transmission through gelatine, the *Gelatine Manufacturers of Europe* (G.M.E.) took the initiative for a validation study on the removal/inactivation capacity of the gelatine manufacturing process. At the time of writing this opinion, only an interim report was available, covering the first 9 months of the study (Inveresk Research International, 1997), as well as a preliminary update of the results after 18 months (Inveresk Research International, 1998).

Two key chemical treatments in the manufacturing process of gelatine were validated for BSE inactivation: the acid treatment and the liming treatment.

Fine crushed bones were challenged artificially with high titres of scrapie infected mouse brain ($\log_{10}$ ID_{50}=7.23) for the acid treatment and $\log_{10}$ ID_{50}= 7.90 for the liming treatment.

The artificially contaminated bones were, after demineralisation, inoculated intracerebraly to susceptible mice to calculate the reduction factors of infectivity in each step of the gelatine manufacturing process.

The acid treatment shows only limited efficiency in the inactivation of potential prion contamination: after 18 months inoculation, the reduction factor was $1.01\log_{10}$ (approx. 10 fold).

The liming treatments after 20 days, 45 days and 60 days, give also partial reduction of potential infectivity of respectively $2.48\log_{10}$, $2.07\log_{10}$ and $2.09\log_{10}$. The level of reduction of infectivity by liming seems not to be associated linearly with the length of incubation.

The final report of this laboratory study should be available early in 1998, but it seems that neither the acid-nor the lime treatment completely inactivate the infectious agent.

Another study is planned by G.M.E. (G.M.E., 1997b) to evaluate the incidence of the extraction, filtration, ion exchange and sterilisation steps on the inactivation of the BSE agent.

The **Pharmaceutical Research and Manufacturers of the America** (PhRMA) accepts that acid treatment and the liming step should substantially reduce any BSE infectivity by at least 10^{-5}. (Based upon the risk assessment carried out by PhRMA

(Bader et al, 1997), one might expect to see one case of n.v.-C.J.D. per million-million patient treatment years as a result of pharmaceutical use of gelatine, under the conditions of sourcing and processing indicated in the report as an example)

The SSC recommends that research on the elimination and inactivation of TSE agents during the gelatine manufacturing process should also be carried out for the production process as a whole, starting with the degreasing step of infected material, and not as individual research studies covering each of the production steps separately and that the results should be compared with the above results. This will make it possible to confirm or infirm the cumulative effect of different sequential treatments.

7. The question

On the basis of what precedes, the working group addressed the following question*: "Can gelatine be considered to be free of BSE infectivity? If not, under which conditions of sourcing of the material (geographical and animal) and/or of type of material used (e.g. specified risk materials and/or age of the animal and/or production process can it be considered as safe?"*

8. Scientific opinion

Preliminary note:

In its opinion of 22-23 January 1998 defining the BSE risk for specific geographical areas, the Scientific Steering Committee has listed the factors contributing to the incident and propagation risks in a geographical area. This list is attached as an annex, for ease of reference. More work needs to be done on the definition of risk regions or countries. The Committee is preparing a further opinion on the geographical aspects of BSE risks.

The four classes of the geographical aspect of BSE risks used in the opinion hereafter, are therefore indicative and, for the time being, are: "high risk countries", "lower risk countries", "countries considered free of BSE or classified as at negligible risk" and "Countries with an unknown TSE status". The corresponding wording of the opinion hereafter may thus possibly have to be revised / updated in accordance with the forthcoming Scientific Steering Committee opinion on the geographical aspects of TSE/BSE risks and on the criteria to be applied for the evaluation of the TSE status of a country.

The Scientific Steering Committee adopted the following opinion on the safety of gelatine:

" 1. Definitions:

- *For the purpose of the present opinion, gelatine is defined as a mixture of polypeptides obtained by partial hydrolysis of the collagen contained in bones and skins from bovines and/or pigs after successive treatments: degreasing, acid treatment, alkaline treatment (liming), washing, filtration, ion exchange, sterilisation and oxidising treatment.*

- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem, inspection and that are*

certified and identifiable as fit for human consumption on the basis of the existing national and EU legislation. The Scientific Steering Committee stresses that positive identification of material not fit for human consumption should be possible, to avoid possible entering of such material in the food or feed chains.

– *Unless otherwise specified, the wording "Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.*

– *"Industrial use" means that the end product is not for direct nor indirect human or animal consumption or use, including not as a cosmetic nor as a pharmaceutical product.*

– *Appropriate production processes. An example of an appropriate production process is: bones finely crushed and degreased with hot water and treated with dilute hydrochloric acid (approximately 4% and pH <1.5) over a period of five days, followed by an alkaline treatment of saturated lime solution (pH >12.5) for a period of approximately 50 days with a sterilisation step of 140°C during 4 seconds. Regarding the sterilisation step, the SSC notes that the appropriate technique should be used, as its efficacy in contributing to the elimination / inactivation of a TSE agent will also depend upon the time needed to reach the temperature, the duration of the cooling and the atmospheric pressure during the process.*

  Equivalent methods with a demonstrated efficacy in terms of eliminating TSE agents may be acceptable. However, such methods must be evaluated and acknowledged approved on a case by case basis.

– *For "special grade gelatine",, the ruminant raw materials should be sourced from either:*
  a) geographic areas where there is reliable evidence of zero to negligible risk, or:
  b) animals from a no-risk offspring population within a given nation or region, because of a number of criteria excluding the possible risk of infectivity are being met: age, traceability of the descendence of the individual animal and of the herd of origin, no history of feeding feedstuffs of animal origin, etc.

  In either case, materials should originate from dedicated production lines, but these could be lines used previously for more general purposes provided that there is a "clean-out" before the start of a dedicated production run.

2. *Because of existing evidence of the possible presence of remaining impurities,*

   and given the fact that the number of critical points[6] in the whole production chain is quite large and that their monitoring may not always be easy and evident,

6 In terms of possible risk for remaining BSE infectivity in the final product

the Scientific Steering Committee is of the opinion that the optimum level of safety can obtained from a combination of safe source of raw material used and a well documented process with defined minimum level of treatment.

3. *The Scientific Steering Committee strongly recommends that gelatine manufacturers implement and respect HACCP[7] procedures. It is essential to identify and describe hasards and critical points for the different processes utilised in gelatine production. Two of these points are the traceability and treatment at origin (e.g., removal of specified risk materials) of the raw material.*

4. *The sections of opinion hereafter cover the approach to be followed if the risk of infectivity in the remaining impurities is to be reduced to the lowest possible level. As an alternative, a more detailed quantitative risk analysis should be carried out to assess the remaining risk for a population or individual. Such assessment would depend upon:*

   - *type of final product and infectivity reduction capacity of the production procedure;*
   - *the geographical origin of the raw material;*
   - *the type of raw material, including the age of the animals;*
   - *the removal or not of specified risk materials;*
   - *the incidence and propagation components of the BSE borne risk, as specified in the opinion of 22-23 January 1998 of the Scientific Steering Committee, defining the BSE risk for specified geographical areas*

   This assessment requires results of experiments on and justified estimates of reduction factors during the various steps of the production process, from sourcing to marketing. Such data are not always available, as some experiments are still ongoing or only in a planning phase. The Scientific Steering Committee intends to undertake this quantitative risk assessment exercise in collaboration with recognised experts and institutions. They results may eventually change or ask for an update of the recommendations hereafter.

5. *The SSC acknowledges the US-FDA (1997) opinion that can gelatine safely be produced from bovine hides from any country, provided that the bovine hides have not been contaminated with specified risk materials and if they exclude hides from cattle that have signs of neurological disease.*

6. *The raw material should - depending upon the intended end use as listed hereafter- be obtained from appropriate sources (geographical, herd animal and its age), animal species and tissues.*

7. *In any case, the raw materials should be submitted to an appropriate production process, as indicated in the above definition.*

8. ***The end use of gelatine is human consumption as well as cosmetic product.***

   8.1. <u>For countries considered to be 'BSE free or classified as at negligible risk'</u>:

   Raw material (bovine bones and skins) can be used free without removal of specified risk materials when coming from animals certified as fit for human consumption.

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7 Hazard Analysis and Critical Control Points

8.2. For lower risk countries:

Specified risk materials should first be removed to minimise the risks of possible contamination. The origin of the raw bovine materials should be certified to be exclusively from animals which are fit for human consumption.

8.2. For high risk countries:

Given the existing production procedures which do not always permit the tracing back of specified risk materials and their geographical origin, the SSC recommends that no sourcing of bovine raw materials (except hides) from high risk countries is allowed. If hides are used, they should be obtained from animals fit for human consumption. However, in certain circumstances, the risk profile can be changed, e.g., on the basis of age of the animal, the origin (source) of the animal, etc. This could result in bovine material from high risk areas to be possibly acceptable for gelatine production provided those circumstances carry no risk and provided the conditions applicable for lower risk countries are respected.

Material from pigs can be used provided that the animals are certified as fit for human consumption and processed on separate lines in slaughterhouses.

8.4. Countries with an unknown BSE status should be evaluated individually on the basis of a detailed evaluation using appropriate criteria. If no judgement possible, they should be considered as high risk countries.

9. The end use of gelatine in registered pharmaceutical products and for parenteral use.

Gelatine in pharmaceuticals may be administered by the oral topical or parenteral route. In the case of implantable medical devices they may persist at the site of administration for longer periods of time. The standards required for manufacture of gelatine for use in pharmaceuticals may therefore vary according to the route or site of application.

9.1 Gelatine for oral or topical use (excluding ophthalmic use).

The same conditions as for food and cosmetic use set out in paragraph 8 should apply, recognising that pharmaceutical products should confer benefits which outweigh risks. Consideration should be given to the use of a special grade gelatine in topical products where these are likely to be applied to large areas of damaged skin or to open wounds.

9.2. Gelatine for parenteral or ophthalmic administration or for use in implantable devices (including use as excipients in this group of products).

The SSC recommends that a special grade of gelatine should be considered for these products containing gelatine. The conditions set out in the above paragraph 8 should apply and appropriate purification procedures should be used.

Parenterally administered pharmaceuticals and implantable medical devices are available only through a regulatory licensing process, and the benefit/risk determination with respect to the source and process for the manufacture of gelatine should be considered on a case by case basis as a part of that licensing process.

10. The end use of the gelatine is as a reagent in the manufacture of pharmaceuticals.

Where the end products for which gelatine was needed in the manufacturing process, are for parenteral or ophthalmic use or vaccines, the Scientific Steering Committee considers that it would be safer to apply the same stringent controls as set out in above paragraph 9.2. (The state of knowledge on BSE is indeed still developing and the causative agent, its infectivity and distribution in tissues require much further research. Vaccines are a special case as they are administered to healthy subjects for preventive purposes and therefore should carry a minimal risk.)

11. The end use is exclusively industrial *(for example photographical products and miscellaneous technical applications and products)**.***

The raw material should be submitted to an appropriate production process, as indicated in the definition above. Protection measures at workplace to avoid direct contact should be in place. If ingestion or exposure of the gelatine with the human body may be expected under normal conditions of use, the gelatine should comply with the conditions described in the above paragraph 8.

Summary table: the safety of gelatine derived from ruminant bones and from hides possibly contaminated with specified risk materials [8]

END USE:	Human consumption and cosmetic products	Registered pharmaceutical products and parenteral use			Industrial use
		Oral or topological	Parenteral, ophthalmic; implantable product	Gelatine as component in manufacture	
Source: BSE FREE or NEGLIGIBLE RISK	- Fit for human consumption - Appropriate production process	- As for Human consumption and cosmetic products; - Special grade gelatine if applied to large areas of damaged skin or to open wounds; – Regulatory licensing process[11]	- As for Human consumption and cosmetic products; - Special grade gelatine if applied to large areas of damaged skin or to open wounds. – If bovines material is used, it should be of negligible risk; - Appropriate and validated	– Manufacture of products for parenteral or ophthalmic use or for vaccines: – As for implantable products	- Appropriate production process.
Source: LOWER RISK	- Fit for human consumption - SRMs[9] excluded - Appropriate production process				- Appropriate production process;
Source: HIGH	- Exclude: all ruminant materials, except				- Appropriate production process; - Appropri

8 Non contaminated hides are in principle safe. Hides of cattle that have signs of a neurological disease should always be excluded.

9 SRMs or Specified risk materials" refer to all tissues listed in the opinion of the SSC adopted on 8-9.12.97. However, the SSC considers the possibility of making a selection of SRMs on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.

10 In certain circumstances, the risk profile can be changed, e.g., on the basis of age of the animal, the origin (source) of the animal, etc. This could result in bovine material from high risk areas to be possibly acceptable for gelatine production provided those circumstances carry no risk and provided the conditions applicable for lower risk countries are respected

RISK	hides [10]; - Ruminant hides only from animals fit for human consumption; - Pig materials to be processed on separate lines.		purification process; - Regulatory licensing process[11] - Dedicated production lines;		ate protection of workers. - If ingestion or exposure risk: as for human use;
Status unknown	To be evaluated; if no judgement possible: consider as high risk				

[11] For placing pharmaceutical products on the market.

Annex C to the SSC Opinion of 10-20 February 1998

The safety of tallow derived from ruminant tissues

Report and preliminary scientific opinion
adopted at the Scientific Steering Committee meeting of
19-20 February 1998

Report and preliminary scientific opinion on the safety of tallow derived from ruminant tissues

1. Definition of tallow

According to Council Directive 92/5/EEC of 10.02.92, rendered animal fat is fat derived from rendering meat, including bones, and intended for human consumption. Tallow is rendered animal fat from bovine origin.

For the purpose of the present opinion, tallow is defined as fats obtained by pressing or any extraction system down from ruminant tissues which are derived directly from discrete adipose tissue masses, from fat extracted from skeleton muscles, from mechanically recovered meat and from rendered animal waste, including bones.

2. Background

On 8 September 1997, The MDSC/SSC adopted the following opinion on the security of tallow produced from bovine material.

" Tallow is a raw material which is used in the food, feed, medicinal and non-food sector. In the light of actual scientific knowledge on BSE, the question is still open if Tallow could transfer the BSE agent to animals (via the feed-chain) or to man (via the food and non-food chain).

To reach a sufficient degree of security when using tallow, it is therefore necessary that either the material used for the production of Tallow is safe, i.e. not infectious, or that the production process used has shown to actual knowledge that the agent is neutralised.

Concerning the raw material it has to be accepted that, as long as no test is available which allows to diagnose non-clinical BSE cases (pre-mortem), the only way of determining that the basic raw material is safe if a procedure as described by the OIE in Chapter 3.2.13 of the OIE International Zoo-Sanitary Code on BSE, is applied.

In cases where the animal material comes from a country of low risk or from a country controlled by epidemiological surveillance, this raw material has to be classified to be suitable for human consumption. In order to minimise a possibly remaining risk of infectivity of the raw material those parts of the animals which are supposed to carry a high level of infectivity (= the Specified Risk Material SRM, as defined in the corresponding opinion) shall be excluded from the production of tallow.

A third safeguard is a transformation process. So far it was accepted that no infectivity could be found after exposing even infected material over 20 minutes to a temperature of 133°C at 3 bar or an equivalent method with demonstrated efficacy. However, during the International Meat and Bone Meal Conference held in Brussels on 1 and 2 July 1997, it was not excluded that under worst case conditions, traces of infectivity could remain. This implies that the only safeguard at present is the certified origin of the material from which the product is derived AND an appropriate production process following acknowledged production rules.

Keeping in mind the remaining scientific uncertainties the SSC therefore recommends that in all cases the process "133°C, 3 bar, 20 minutes or an equivalent method with demonstrated efficacy" is to be applied, and that an infectivity of the raw material must be reduced to the maximum possible by sourcing (geographical origin or certification of individual animals) and by avoiding the use of specified risk material."

This opinion is line with the opinion adopted on 9 April 1996 by the Scientific veterinary Committee (E.C., 1996), which states:

" (...) Data on tallow have been obtained as part of the study on rendering processes, and show no detectable BSE infectivity in material from all tested systems on bioassay in susceptible mice. New data on inactivation of scrapie agent, however, indicates that only one system evaluated (133°C at 3 bar for 20 minutes) resulted in a product (meat and bone meal) which had no detectable infectivity. Because the initial titre of the agent in the BSE experiment was lower than in the scrapie study, only this latter process can be considered as providing adequate guarantees for the production of tallow.

(...) The following processes are recognised as giving the best possible guarantees:

1. (...)

2. Tallow produced in a process which ensures that all material is subjected to 133°C for at least 20 minutes at 3 bar, followed by filtration to eliminate protein residues."

Since the MDSC/SSC meeting of 8 September 1997, during which opinions on Tallow were adopted, a number of industry associations and third countries submitted a number of comments and technical and scientific dossiers. The main comment is that imposing a process "133°C / 3 bars / 20 minutes" is not reasonable for tallow production. The final product seems to be of inferior quality (discolouring of the material, altering of the fatty acids content, altering of the structural properties of tallow). Normal industrial tallow production processes - even the ones using the lowest time/temperature combinations - and corresponding research have shown to result in a product which is free from detectable TSE infectivity (injection into the brain of mice), even if the source material was highly infective. The explanation of this results seems to lay in the fact that "*because of the proteinaceous nature of the TSE agents they would tend to remain with the cellular residues of meat and bone meal during extraction process, rather than be extracted with the lipids of tallow.*" (WHO, 1995; WHO, 1996; WHO, 1997).

In addition the final results of the 1991-1997 Rendering study became available (MAFF, 1997). This study is often used as a justification for the preceding statement that tallow can be considered safe even if it is submitted to much less harsh conditions. It is also part of the scientific basis of Commission Decisions N° 94/382/CE (repealed) and 96/449/CE.

The thesis that tallow is a safe product is also supported in the Guidelines to minimise the transmission of spongiform encephalopathies in medicinal products issued in 1994 by the German Federal Health Authority (BGA, 1994), which classified tallow in the lowest risk class which includes also milk. Also for the US-FDA, tallow and other fats are considered as non infective (see also the Report

of the International scientific conference on animal meal held in Brussels on 1 and 2 July 1997) (EC, 1997).

On the basis of what precedes, the MDSC/SSC decided during its meeting of 16 October 1997, to create a working group on the safety of tallow. The mandate of the working group is given in annex.

3. Non exhaustive list of relevant scientific and technical material.

The following is a non exhaustive list of technical and scientific documentation relevant to the subject:

A Norman Tate & Co, 1997. Certificate of analysis of remaining moisture and insoluble impurities in tallow from bovine and tallow from sheep origin. (Attached to COLIPA, 1997).

Anonymous, 1995. Bekanntmachung über die Zulassung und Registrierung von Arzneimitten + annexes. Reprint from Pharm.Ind., 57, 12, 261-270.

APAG (European Oleochemicals & Allied Products Group), 1997. Letters to the Scientific Steering Committee secretariat on tallow and on the MDSC/SSC Opinion of 8.09.97 on tallow.

APAG (European Oleochemicals & Allied Products Group), 1997. The safety of tallow derivatives with respect to spongiform encephalopathy. Technical document prepared.

Bader,F., Davis, G., Dinowitz, B., Garfinkle, B., Harvey, J., Kozak, R, Lubiniecki, A.., Rubino, M., Schubert, D., Wiebe, M., Woollet, G. 1997. Assessment of Risk of Bovine Spongiform Encephalopathy in Pharmaceutical Products. Pharmaceutical Research and Manufactures of America (PhRMA) - BSE Committee. Technical document, Washington D.C. (USA). 58 pp

BGA (German federal health Office), 1994. BSE and Scrapie - German Federal health Office (BGA) on Safety Measures to be adopted for Medicinal Products. In: Drugs made in Germany, Vol.37 (N°2): pp 36-49.

Brown, P., Wolff, A., Liberski, P.P., Gajdusek, D.C., 1990. Resistance of scrapie infectivity to steam autoclaving after formaldehyde fixation, and limited survival after ashing at 360°C: practical and theoretical implications. J.Infect.Dis. Vol.161: pp 467-472.

Bruce, M., Chree, A., McDonnell, I., Foster, J., Pearson, G., Fraser, H., 1994. Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier. Philosophical Transactions of the Royal Society of London, Vol. 343: pp 405;411.

COLIPA, 1997. The use of tallow derivatives in cosmetic products: a safety evaluation. (Paper prepared by COLIPA, the European Cosmetic Toiletry and Perfumery Association, in collaboration with various organisms.)

Detlev, R., Kellings K., Post, K., Wille, H., Serban, H., Groth, D., Baldwin, M.A., Prusiner, S.B., 1996. Disruption of Prion Rods Generates 10-nm Spherical Particles Having High ?-Helical Content and Lacking Scrapie Infectivity. Journal of Virology, March 1996, Vol.70. (3):1714-1722

Dickinson, A.G., Outram, G.W., Taylor, D.M., Foster, J.D., 1989. Further evidence that scrapie agent has an independent genome. In: Unconventional virus diseases of the central nervous system. Paris 2-6 December 1986, pp 446-459. Edited by Court, L.A., et al., 1989. Fontenay-aux Roses (France).

Dickinson, A.G., Taylor, D.M., 1978. Resistance of scrapie agent to decontamination. New England Journal of Medicine, Vol.299, pp. 1413-1414.

Die Pharmazeutische Industrie, 1991. Spongiforme Encephalopathien und Arzneimittel: Sachstand und Grundzüge einer Risikobetrachtung. Reprint from Pharm.Ind., 53, 7, 613-623.

E.C. (European Commission), 1996a. The Scientific Veterinary Committee. Opinion of 9 April 1996 on the risk associated with certain animal products in relation to Bovine Spongiform Encephalopathy (BSE).

E.C. (European Commission), 1996b. The Scientific Veterinary Committee. Opinion of 18 April 1996 on the results of the rendering study Phase II - Scrapie.

E.C. (European Commission), 1996c. The Scientific Veterinary Committee. Report on the Control of risks from BSE- and Scrapie-infected material in regard to protection of public and animal health. Adopted on 21 October 1996.

E.C. (European Commission), 1997a. The opinion of 24 June 1997 of the EC Scientific Committee Cosmetology;

E.C. (European Commission), 1997b. Opinions on the safety of tallow and of tallow derivatives, adopted by the Multidisciplinary Scientific Committee / Scientific Steering Committee on 8 September 1997.

Eleni, C., Di Guardo, G., Agrimi, U., 1997. Encefalopatia Spongiforme Bovina (BSE): Analisi del Rischio in Italia. Large Animals Review, Vol.3 (N°4): pp. 5-15.

EMEA (The European Agency for the Evaluation of Medicinal Products, 1996. the opinion of 16 April 1996 of Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of medicinal Products (EMEA).

EMEA (The European Agency for the Evaluation of Medicinal Products, 1997. Revised draft 14 - rev.1 (2nd September 1997) of the Committee for Proprietary Medicinal Products (CPMP) Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Kimberlin R.H., Walker, C.A., Millson, G.C., Taylor, D.M., Roberston, P.A., Tomlinson, A.H., Dickinson, A.G., 1983. Disinfection studies with two strains of mouse-passages scrapie agent. J.Neurol.Sci.,Vol. 59: pp 355-369.

Kimberlin, R.H., 1994. Presentation in: Transmissible spongiform encephalopathies: a consultation with the Scientific Veterinary Committee of the European Communities. Brussels, 14-15 September 1993. Kluwer Academics. Dordrecht, p. 455**.**

Kimberlin, R.H., 1996. Bovine spongiform encephalopathy and public health: some problems and solutions in assessing the risks. In: **Court, L. and Dodet, B., Eds., 1996.** Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Proceedings of the IIIrd International Symposium on Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Elsevier, Paris, 16 pages.

Lasmézas, C.I., Deslys, J.-P., Demaimay, R., Adjou, K.T., Hauw, J.-J., Dormont., D., 1996. Strain specific and common pathogenesis events in

murine models of scrapie and bovine spongiform encephalopathy. Journal of General Virology, Vol.77: pp 1601-1609.

MAFF (Ministry of Agriculture and Fisheries, UK), IAH (Institute of Animal Health), Prosper De Mulder, CNEVA (France), 1997. Inactivation of the BSE and scrapie agents during the rendering process. Final report of the Study contract N° 8001 CT90 0033 co-funded by the European Commission and MAFF.

OIE (Office International des Epizooties), 1997. Bovine Spongiform Encephalopathy (BSE). Chapter 3.2.13 of the OIE International Zoo-Sanitary Code on BSE.

Piva, G., 1997. Unpublished results of 3 laboratory determinations of nitrogen impurities in fat (tallow + lard) for animal nutrition. Istituto di Scienze degli Alimenti e della Nutrizione. Facoltà di Agraria, U.C.S.C., Piacenza (Italia).

Riedinger, O., 1998. Stellungnahme zum vorläufigen Arbeitspapier der "BSE/TSE-working group", das unter Federführung van Prof.Piva am 12.02.98 in Brüssel beraten soll. Discussion paper. 10pp

Robinson, M.M., Hadlow, W.J., Huff, T.P., Wells, G.A., Dawson, M., Marsh, R.F., Gorham, J.R., 1994. Experimental infection of mink with bovine spongiform encephalopathy. Journal of General Virology, Vol.75, pp.2151-2155.

Taylor, D., 1997. Current science on inactivation of TSE. (Extract from a public presentation). (attached to COLIPA, 1997)

Taylor, D.M., Fraser, H., McConnell, I., Brown, D.A., Brown, K.L., Lamza, K.A., Smith, G.R.A., 1994. Decontamination studies with the agents of bovine spongiform encephalopathy and scrapie. Archives of Virology, Vol. 139: pp. 313 - 326.

Taylor, D.M., Woodgate, S.L., Atkinson, M.J., 1995. Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. Veterinary Record, Vol.137: pp.605-610.

Taylor, D.M., Woodgate, S.L., Fleetwood, A.J., Cawthorne, R.J.G., 1997. The effect of rendering procedures on scrapie agent. Veterinary Record, Vol.141, pp 643-649

UNEGA (European Animal Fat Processors Association), 1997a. Tallow and Animal Fats. Summary technical documentation.

UNEGA, 1997b. Letter by the UNEGA president to DGVI, including information on the level of "moisture and impurities" that can be accepted in tallow after filtering.

WHO (World health Organisation), 1995. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies. Geneva, 17-19 May 1995. Document WHO/CDS/VPH/95.145.

WHO (World health Organisation), 1996. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies.(With the participation of FAO and OIE) Geneva, 2-3 April 1996. Document WHO/EMC/DIS/96.147.

WHO (World health Organisation), 1997. Report of a WHO consultation on Medicinal and other Products in Relation to Human and Animal Transmissible

Spongiform Encephalopathies.(With the participation of the Office International des Epizootie, OIE) Geneva, 24-26 March 1997.

Wilesmith, J.W., Wells, G.A.J., Cranwell, M.P., Ryan, J.B.M., 1988. Bovine spongiform encephalopathy: epidemiological studies. Vet.Rec., Vol.123: pp.638-644.

Wilesmith, J.W., Ryan, J.B., Atkinson M.J., 1991. Bovine spongiform encephalopathy: epidemiological studies on the origin. Vet.Rec., Vol.128, pp.199-203..

Woodgate, S., 1997. TSE Agents: Inactivation by rendering systems and the role of inactivation research on new processing regulations for the European rendering industry. Conference paper. Lipidex 97: 18-21 March 1997 Symposium 1 Tradefair. Antwerp (B). (attached to COLIPA, 1997)

It may be noted that the following documents provide more or less detailed descriptions of production processes and/or information on the origin of the material and the destination of the final product:

APAG (European Oleochemicals & Allied Products Group), 1997. The safety of tallow derivatives with respect to spongiform encephalopathy. Technical document prepared for the Scientific Steering Committee.

MAFF (Ministry of Agriculture and Fisheries, UK), IAH (Institute of Animal Health), Prosper De Mulder, CNEVA (France), 1997. Inactivation of the BSE and scrapie agents during the rendering process. Final report of the Study contract N° 8001 CT90 0033 co-funded by the European Commission and MAFF. Registered at the SSC secretariat as Document

Taylor, D.M., Woodgate, S.L., Atkinson, M.J., 1997. Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. Veterinary Record, Vol.137: pp.605-610. (Provides the key-results of MAFF et al., 1997.)

UNEGA (European Animal Fat Processors Association), 1997. Tallow and Animal Fats. Summary technical documentation.

4. On the production of tallow

In order to express an opinion on the safety of tallow it is important to keep into account a number of aspects of the fat production methodologies and conditions.

4.1 **Production of tallow** (See also UNEGA, 1997a and UNEGA 1997b)

Tallow and other animal fats are manufactured primarily from the animal materials arising from the meat industry (slaughterers, cutting plants and butchers shops) which are not required for direct human consumption. Raw materials such as subcutaneous, abdominal and intermuscular fats, organ fats, offal and bones are by far the main sources of tallow and other animals fats. Some sectors of the rendering industry utilise materials from animals rejected at ante or post mortem inspection and farm-dead animals (fallen stock).

Tallow is produced from animal tissues containing fat by a variety of processes called 'rendering ' or 'fat melting'. Fat melting is a term usually reserved for the processing of edible fats. However, rendering is the term used in some countries, notably Germany and the Netherlands, only for the processing of inedible and 'high risk' animal waste which will contain fallen-stock . In many other countries rendering is used to describe the whole

range of animal by-products processing operations. (Collins English Dictionary: to render - to extract fat from meat by melting).

Typically the raw materials are minced and heated, mechanically agitated and the moisture evaporated or separated. The lipid fraction is separated from the protein by centrifugation and pressing. Processing conditions vary in the different fat melting and rendering systems which will be determined by the type and quality of the raw materials being processed and the desired quality characteristics of the tallow's end use.

Specifications of tallow as a commodity are typically set for titre (solidification temperature), free fatty acid level, peroxide value, colour, moisture content, insoluble impurities, unsaponifiable matter, etc. In general, the freshness of the raw material, the origin and the nature of the tissues will determine the end quality of the tallow or animal fat. Fresh adipose tissue and bones is needed to give the high quality specification of colour, free fatty acid and peroxide levels required for edible purposes and toilet soap manufacture, for example. Less fresh material or the presence of significant quantities of offals in the raw material mix will result in fat with darker colour and higher free fatty acid levels - generally suitable for animal feeds or further processing by the oleochemical industry to produce chemical derivatives.

4.2 **The separation of fat from proteins** and from all the other impurities can be realised through the following steps:

- ***centrifugation:*** highly efficient process, but it doesn't always guarantee the complete elimination of the residues;
- ***filtration***: some methodologies of microfiltration on ceramics, on filtering beds (earth filtering, clays, bentonite, montmorillonite, philipsite) (20-25µ) with appropriate filtration co-adjuvants (celite) are available. These methodologies are effective and lead to very low residues levels. Afterwards it is necessary to eliminate the filtration supports (filtering beds and co-adjuvants) which cause costs and environmental problems.
- ***treatment with phosphoric acid*** homogenate with a phosphoric acid water solution and afterwards centrifugation. Residual nitrogen levels are approximately less than 0.01%.

All these processes are usually realised at a temperature around or over 80°C.

4.3 **Maximum impurities acceptable level**. Under the assumption that it is not scientifically acceptable to make the hypothesis of zero nitrogen residues, it is necessary to give indications of the fat residual nitrogen acceptable levels.

The requirement of imposing a maximum acceptable value of nitrogen residues as the maximum molecular weight of remaining peptides and polypeptides is not straightforward. These peptides and polypeptides residues are probably not present in the lipid fraction because, due to their water solubility, they should have been pushed away in the first step of the process. It is instead credible that the residual protein fractions mainly come from cellular protein fragments of the fatty tissue.

A maximum level of total insoluble impurities below a given content (e.g. 0.15% in weight, to be confirmed) and/or a maximum level of nitrogen

(determined according to the Kjeldhal method, to be confirmed) and the possible residual peptides or polypeptides having a molecular weight below 10.000 Dalton may therefore be proposed to indicate the maximum impurities acceptable level. Regarding the nitrogen levels, the not published laboratory analyses (Piva, 1997) resulted in Nitrogen levels of 0.01 - 0.02 %.

5. Some considerations regarding the safety of tallow.

Regarding the safety of tallow, the working group has made the following considerations:

- Wilesmith et al. (1988) indicated already that the geographical variation in the incidence of BSE in the UK is not consistent with the distribution and use of tallow in cattle feed.
- Normal industrial tallow production processes - even the ones using the lowest time/temperature combinations - and corresponding research have shown to result in a product which is free from detectable TSE infectivity (injection into the brain of mice), even if the source material was highly infective. (See also Taylor et al., 1995; Taylor et al., 1997; MAFF et al., 1997).
- The explanation of the preceding result seems to lie in the fact that "*because of the proteinaceous nature of the TSE agents they would tend to remain with the cellular residues of meat and bone meal during extraction process, rather than be extracted with the lipids of tallow.*" (WHO, 1995).
- Although tissues with high titres of infectivity will be more difficult to decontaminate than those with low titres, there are no data that show any difference between the scrapie and BSE agents in terms of their susceptibility to inactivation by chemical or physical methods.. Therefore, although the degree of survival of infectivity was greater during the study of rendering processes spiked with scrapie-infected sheep-brain (Taylor et al., 1997), compared with BSE-infected bovine brain (Taylor et al., 1995), this was likely to be due to the fact that the scrapie-spiked raw materials contained $10^{1.4}$ ID_{50}/G more infectivity than the BSE -spiked raw materials. This would imply that one of the bases of the ScVC opinion of 9.04.96 to declare *133°C at 3 bar for 20 minutes as the only process that can be considered as providing adequate guarantees for the production of tallow*, is not relevant (anymore).
- Apart from the major experiment run in Edinburgh (Taylor et al., 1995; MAFF, 1997; Taylor et al., 1997), the number of other scientific experiments looking into the safety of tallow with regard to TSEs is, to the knowledge of the Scientific Steering Committee, rather limited if not nihil. Also, the experiment, because of its scope, size and duration, has not been repeated in other laboratories. Finally, the experiments were simulations carried out at a pilot scale and the extrapolation of the results (scaling up) into the real operational industrial conditions may therefore not be automatic. No test results, confirming the hypothesis that tallow is 100% safe, are available from operational rendering plants. On the other hand, the above pilot-scale experiments were not simply laboratory approximations of rendering processes, but were carried out in actual (although pilot-scale) rendering equipment. In collaboration with the industry it was determined how the pilot-scale equipment could be operated to provide a realistic representation of what occurs in full-scale rendering. Also, most validation studies done on to the safety of a wide variety of biopharmaceutical products with respect to TSE

agents, are almost always carried out on scaled down versions of the manufacturing processes that are spiked with TSE agents.

- The mice infection tests which are in most cases carried out to detect TSE infection, may not be (fully) representative for a system of homologous detection between animals of the same species (e.g., from bovine to bovine).The sensitivity of the mouse bioassay for assaying TSE agents from cattle or sheep will be compromised by the species barrier. Cattle-to-cattle transmission of BSE by intracerebral route is known to be about 1.000-fold more effective than cattle-to-mouse transmission by the same route (unpublished data from the UK Central Veterinary Laboratory at Weybridge). Superficially, this might appear to compromise any conclusions drawn from the rendering studies with regard to the safety of tallow. However, in assessing risks related to the consumption of tallow, the much greater efficiency of establishing infection in mice by the intracerebral (compared with the oral) route of infection must be considered. For example, the difference in efficiency between these two routes for scrapie in mice is 100.000-fold (Kimberlin, 1996). Also, it has been calculated that the transmission of BSE to mice by the oral route is 200.000-fold less efficient than by intracerebral challenge (Kimberlin, 1994). These data seem to indicate that the negative results from the mouse bioassays of tallow in BSE and scrapie-spiked rendering studies can be viewed with a considerable amount of confidence with regard to any risk from infection by its consumption. On the other hand, however, certain strains of natural scrapie are transmitted as easy by the peripheral as by the central route and, for example, the infection of mink by the BSE agent is almost equally effective by the oral route as by the mixed parenteral/intracerebral route (Robinson et al., 1994). The Scientific Steering Committee notes that the scientific discussion on the absolute and relative differences in infectivity according to the way of transmission (oral or central) and depending upon the species barrier, is not yet conclusive and is still ongoing.
- Depending upon the strain and the host, it is possible to have differences in incubation times, pathogenesis, distribution of the lesions in the central nervous system, amount of infective PrP^{Res} and its location inside the central nervous system, etc. (e.g., Lasmézas et al., 1996; Kimberlin et al., 1983; Dickinson et al., 1989; Bruce et al., 1994). There are also known differences between some strains of scrapie agent in terms of their thermo-stability (Dickingson and Taylor, 1978; Kimberlin et al., 1983). To date, however, there are no compelling data to indicate that BSE agent is more thermo-stable than scrapie agent.
- The quality of the result of filtration (in terms of remaining level of impurities) depends upon the quality of the raw tallow before filtration (for example, from which type of tissues it was derived from) and depends also upon the type of production process used (for example, mechanical pressure combined with heat treatment or tallow obtained after a heat treatment).

6. The question.

On the basis of what precedes, the working group addressed the following key question:

" Can tallow be considered to be free of TSE infectivity, regardless of the source of the material (geographical and animal), regardless of the type of material used (e.g., SRMs), regardless the age of the animal and regardless of the production process,

but provided it is free from proteinaceous material as a result of appropriate purification?"

7. Scientific opinion

Preliminary note:

In its opinion of 22-23 January 1998 defining the BSE risk for specific geographical areas, the Scientific Steering Committee has listed the factors contributing to the incident and propagation risks in a geographical area. This list is attached as an annex, for ease of reference. More work needs to be done on the definition of risk regions or countries. The Committee is preparing a further opinion on the geographical aspects of BSE risks.

The four classes of the geographical aspect of BSE risks used in the opinion hereafter, are therefore indicative and, for the time being, are: "high risk countries", "lower risk countries", "countries considered free of BSE or classified as at negligible risk" and "Countries with an unknown TSE status". The corresponding wording of the opinion hereafter may thus possibly have to be revised / updated in accordance with the forthcoming Scientific Steering Committee opinion on the geographical aspects of TSE/BSE risks and on the criteria to be applied for the evaluation of the TSE status of a country.

The Scientific Steering Committee adopted the following opinion on the safety of tallow:

1. Definitions:

- *For the purpose of the present opinion, tallow is defined as fats obtained by pressing or any extraction system down from ruminant tissues which are derived directly from discrete adipose tissue masses, from fat extracted from skeleton muscles, from mechanically recovered meat and from rendered animal waste, including bones.*
- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem, inspection and that are certified and identifiable as fit for human consumption on the basis of the existing national and EU legislation. The Scientific Steering Committee stresses that positive identification of material not fit for human consumption should be possible, to avoid possible entering of such material in the food or feed chains.*
- *An "appropriate purification process" can consist of adequate filtering and/or centrifugation and/or coagulation and should result in maximum levels of remaining total insoluble impurities of 0.10-0.15 % in weight or residual nitrogen below 0.02 %. and the possible residual peptides or polypeptides should have a molecular weight below* x *Dalton [to be determined].*

– *Unless otherwise specified, the wording "Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.*

– *The wording "133°C/20'/3 bars" refers to production process conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. Regarding the fact whether they should be realised under batch or continuous conditions, the Scientific Steering Committee is of the opinion that there will be no difference in the effectiveness provided the time/temperature/pressure parameters are effectively achieved in every part of the material being processed. Equivalent processes should be evaluated and acknowledged on a case by case basis.*

– *"Industrial use" means that the end product is not for direct nor indirect human or animal consumption or use, including not as a cosmetic nor as a pharmaceutical product.*

2. *In principle, tallow is safe **after appropriate purification**. But due to the documented possible presence of impurities, and depending upon the intended end-use, the raw material should be obtained from appropriate sources (geographical, herd, animal and its age, ...), animal species and tissues. Where required the appropriate production processes should be used.*

3. *The Scientific Steering Committee strongly recommends that manufacturers implement and respect HACCP[12] procedures. It is essential to identify and describe the hazards and critical points for the different processes utilised in production. Two of these points is certainly the traceability and treatment at the origin (e.g., removal of specified risk materials) of the raw material.*

4. *The sections of opinion hereafter cover the approach to be followed if the risk of infectivity in the remaining impurities is to be reduced to the lowest possible level. As an alternative, a more detailed quantitative risk analysis should be carried out to assess the remaining risk for a population or individual. Such assessment would depend upon:*
   - *type of final product and infectivity reduction capacity of the production procedure;*
   - *the geographical origin of the raw material;*
   - *the type of raw material, including the age of the animals;*
   - *the removal or not of specified risk materials;*
   - *the incidence and propagation components of the BSE borne risk, as specified in the opinion of 22-23 January 1998 of the Scientific Steering Committee, defining the BSE risk for specified geographical areas*

   This assessment requires results of experiments on and justified estimates of reduction factors during the various steps of the production process, from sourcing to marketing. Such data are not always available, as some experiments are still ongoing or only in a planning phase. The Scientific Steering Committee intends to undertake this quantitative risk assessment

12 Hazard Analysis and Critical Control Points

exercise in collaboration with recognised experts and institutions. They results may eventually change or ask for an update of the recommendations hereafter.

5. Four different groups of end-uses of tallow are considered hereafter.

5.1. The end use of the tallow is for human or animal consumption or application.

5.1.A. The animals from which the raw material is derived, are fit for human consumption.

a) For countries considered to be 'BSE free or classified as at negligible risk', raw material from animals fit for human consumption, can be used without conditions regarding minimal production processes or removal of specified risk materials. As a measure of additional precaution, the Scientific Steering Committee recommends that the tallow should be submitted to an appropriate and validated purification process.

b) For lower risk countries, the use of specified risk materials should be excluded. The origin of the raw material should be fit for human consumption. The tallow should be submitted to an appropriate and validated purification process.

c) For high risk countries the use of specified risk materials should be excluded. The origin of the raw material should be certified to be exclusively from animals which are fit for human consumption. The tallow should be submitted to an appropriate and validated purification process. The tallow obtained from rendering a mixture of tissues and offals (excluding tallow directly obtained from discrete adipose tissues) should be submitted to a process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. .

d) Countries with an unknown TSE status should be evaluated individually on the basis of a detailed evaluation using appropriate criteria. As long as its status remains unknown, a region or country is considered as a high risk one.

5.1.B. The animals from which the raw material is derived, are not fit for human consumption.

The Scientific Steering Committee considers that the questions relative to the risks related to the use of fallen stock, condemned carcasses, sick animals, laboratory animals, etc. should be specially addressed. This discussion should also address the possible minimal processing conditions[13] of these materials. ***(See also paragraph 6 of this opinion.)***

Until such opinion becomes available, raw material not fit for human consumption (excluding clinical TSE cases which should be excluded anyway) could be used ***as animal feed only, provided*** *the*

13 For example 133°C during 20 minutes at 3 bars

specified risk materials were removed, and after appropriate purification of the tallow. In addition, the tallow should be submitted to a process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process .

5.2. The possible end use of the tallow is as an injectable product.

The Scientific Steering Committee has examined the existing licensed uses in the E.U. of tallow and is not aware of any licensed use of tallow as an injectable product. If it were to be used as such, the SSC would need to issue an additional opinion.

5.3. The end use of the tallow is industrial (with the exception of tallow derivatives).

5.3.A. The animals from which the raw material is derived, are fit for human consumption.

The animals from which the material is derived, should be certified to be fit for human consumption. The tallow should be appropriately purified.

5.3.B. The animals from which the raw material is derived, are not fit for human consumption.

The tallow should be appropriately purified. In addition, the material should be submitted to minimal conditions of 133°C at 3 bar or equivalent process.

If the intended end use cannot be verified and controlled to exclude any human or animal consumption or use, then the conditions outlined in the preceding paragraph 1.A should apply also for tallow for industrial or technical use.

5.4. The end use of the product is as raw material for the production of tallow derivatives. *The working group confirms the opinion of the MDSC/SSC of 8 September 1997, namely that tallow derivatives can be considered to be safe provided:*

a) the raw material is fit for human or animal consumption (see previous item 4.1.A), or:

b) provided, regardless of the source of the material and regardless of the type of material, the production process uses the appropriate, validated and scientifically most up-to-date methods in terms of inactivating the BSE agent. Several amongst them have been listed in the scientific opinion of the Scientific Committee on Cosmetology[14] (for cosmetic products) and in the opinions of Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) [15] (for medicinal products). The working group recognises that other methods may exist, but they should be evaluated and acknowledged as safe on a case by case basis.

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14 Of 24 June 1997

15 Of 16 April 1996 and of 17 December 1997.

6. *The Scientific Steering Committee, in its capacity of co-ordinator of multidisciplinary questions, further recommends that additional opinions are prepared by the appropriate Scientific Committees, on the following subjects:*

   – *the protection against the risk of infectious agents or non conventional transmissible agents entering the human food or animal feed chains via raw material (for example as exotic/zoo animals, dead animals, condemned carcasses, sick animals, laboratory animals). This discussion should also address the possible minimal processing conditions[16] of these materials.*

   – *whether and under which conditions can tallow be used as a source of fat in milk-replacers for calves (and possibly lambs and kids). It may indeed appear to be prudent to consider to exclude this tallow from the high-fat milks fed to young calves.*

16 For example 133°C during 20 minutes at 3 bars

Summary table: the safety of tallow derived from ruminant tissues

Intended end-use: Þ		**Human or animal use**	**Animal use**	**Industrial use**[17]	
Animal class: Þ		**Fit for human consumption**	**Non fit for human consumption**	**Fit for human consumption**	**Non fit for human consumption**
Conditions common to all sources: Þ		- certified as fit for human human consumption - purification	- SRMs18 excluded - Purification - 133°C/20'/3bar or equivalent	- certified as fit for human human consumption - purification	- purification - 133°C/20'/3 bars or equivalent
ORIGIN	**BSE FREE OR NEGLIGIBLE RISK**				
	LOWER RISK	- SRMs excluded[18]			
	HIGH RISK	- SRMs [18] excluded - if rendering a mixture of tissues[19]:133°C/20'/3 bar or equivalent.			
	STATUS UNKNOWN	To be evaluated; if no judgement possible: consider as high risk			
Notes			See text on risk animals and on feeding of calves.	*If human or animal consumption or use cannot be excluded, then the conditions outlined for human and animal use apply.*	

Note: Tallow derivatives are conisdered safe, provided they were obtained from raw tallow produced according to the condition listed in the column "Human or animal use" or if appropriate and validated production processes were used, for example the ones listed in the Scientific Committee Cosmetology opinion of 24.06.97 or in eth EMEA opinions of 16.04.96 and 17.12.97.

17 "Industrial use" means here that the end product is not for direct nor indirect human or animal consumption or use, including not as a cosmetic nor as a pharmaceutical product.

18 The wording "SRMs or Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC considers the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.

19 Excluding for tallow directly obtained from discrete adipose tissues.

The safety of meat and bone meal from mammalian animals naturally or experimentally susceptible to Transmissible Spongiform Encephalopathies

Report and preliminary scientific opinion
adopted at the Scientific Steering Committee meeting of
19-20 February 1998

Report and preliminary scientific opinion on the safety of meat and bone meal from mammalian animals naturally or experimentally susceptible to Transmissible Spongiform Encephalopathies

1. Definition of meat and bone meal derived from mammalian animals.

For the purpose of the present opinion meat and bone meal derived from mammalian animals are defined as processed animal protein intended for animal consumption which has been treated so as to render it suitable for direct use as a feeding stuff or as an ingredient in a feeding stuff for animals.

In the frame of the present report, rendering means any processing of slaughter by-products, animals unfit for human consumption or meat scraps for the production of meat and bone meal. The term includes the collection of such materials and subject them to minimal processing, or distribute them to firms other than renderers whose intended use for the products may include animal feed. The term includes also blending animal protein products.

2. Background

a) On the basis of a large experiment carried out between 1991 and 1997 (often referred to as "the rendering study", see Taylor et al., 1995; MAFF et al., 1997), the process conditions of 133°C during 20 minutes at 3 bar are confirmed to result in a safe product. This is acknowledged in various opinions of the Scientific Veterinary Committee (E.C., 1996), for example:

- on 18.04.96: : *"(...) The only method known to be effective at present is heat treatment at 133°C at 3 bar for 20 minutes. It was noted that it may be possible to achieve the same parameters in a continuous system, although data was not provided. The Committee considers that any system which is proven to be operating to the stated parameters will give a product of equivalent safety, irrespective of whether it operates as a batch or continuous system."*

- on 21.10.1996: *"The ScVC recommends that minimum standards for processing waste of mammalian origin to produce meat-and-bone meal (equal or greater than processing at 133°C, 3 bar for 20 min.) should be immediately put in place. (...) Various options were considered which could reduce any risks for animal health (and public health in the long term) in the interim period before the new standards are fully implemented. These include:*

  a) (...), b) (...), c) the exclusion of the highest risk ruminant tissues from rendering systems, i.e. a minimum exclusion of specified risk materials; d) (....)"

b) On 18 July 1996, the European Commission adopted Decisio n N° 96/449/EC on the approval of alternative waste treatment systems for processing animal waste with a view to their inactivation of spongiform encephalopathy agents. This Decision defines the minimum parameters for the processing of animal waste excluding fats as: a maximum particle size of 50 mm, a temperature higher then 133°C, a duration of 20 minutes and a pressure (absolute) of 3 bar. Processing may be carried out in batch or continuous system.

c) The so named "Report of the Committee Dormont" of July 1996 states (République Française, 1996):

"(...) The treatment consisting of a discontinuous process of 133°C / 3 Bars / 20 minutes of particles of 50 mm obtained from condemned carcasses (in French: "cadavres de saisies d'abattoir") *and from the central nervous system, should not be considered as capable of inactivating totally the agent of sub-acute transmissible spongiform encephalopathies. Indeed:*

- *the laboratory experiments have shown that the thermal treatment at 133°C during 20 minutes on its own cannot guarantee the sterility of the product regarding non conventional transmissible agents* (in French: Agents transmissibles non conventionnels, ATNC) *and that its efficacy could vary significantly according to the state of desiccation of the product and its content with lipids (Brown et al., J.Inf.Dis., 1990; Wight and Taylor, The Lancet, June 1993; Taylor et al., Veterinary Record, December 1995);*
- *the published works relate to experiments using limited volumes of material; hence the results cannot be extrapolated with certainty to industrial volumes.*

(...) the [Dormont] *Committee recommends the evaluation of procedures susceptible of reinforcing the efficacy of the thermal treatment. (...) On the other hand, the efficacy of a delipidation with solvents followed by a thermal treatment, seems important to be evaluated in comparison with the sole thermal treatment. (...) In a more general way, and taking into account the multitude and complexity of the* [existing] *processes, the* [Dormont] *Committee recommends an homologation* [of production processes] *on a case by case basis. The Committee also recommends an homologation of the machinery used in the inactivation processes. (...)*

d) The International Scientific Conference on Meat and Bone Meal (Brussels 1&2 July 1997) (E.C., 1997) addressed the issued related to the inactivation / elimination of the BSE infective agent during the production process of MBM. The Verbatim of this conference is provided as E.C. (1997). Referring to discussions held during the conference, the opinion on Tallow adopted on 8.09.97 by the SSC stated:

"(...) A third safeguard is a transformation process. So far it was accepted that no infectivity could be found after exposing even infected material over 20 minutes to a temperature of 133°C at 3 bar or an equivalent method with demonstrated efficacy. However, during the International Meat and Bone Meal Conference held in Brussels on 1 and 2 July 1997, it was not excluded that under worst case conditions, traces of infectivity could remain. This implies that the only safeguard at present is the certified origin of the material from which the product is derived AND an appropriate production process following acknowledged production rules."

e) It can thus be concluded that a production process which respects the conditions of "a maximum particle size 50 mm, a process of 133°C at 3 bars during 20 minutes" is presently the most appropriate one for inactivating / eliminating the BSE infective agent when producing animal derived products

such as MBM, but these conditions as such do not fully guarantee a totally safe product if the raw material was highly contaminated.

On the basis of what precedes, the MDSC/SSC decided during its meeting of 16 October 1997, to create a working group on the safety of Meat and Bone Meal. The mandate of the working group is given in annex.

3. Non exhaustive list of relevant scientific and technical material.

The following is a non exhaustive list of technical and scientific documentation relevant to the subject:

Anonymous, 1995. Bekanntmachung über die Zulassung und Registrierung von Arzneimitten + annexes. Reprint from Pharm.Ind., 57, 12, 261-270.

Bader,F., Davis, G., Dinowitz, B., Garfinkle, B., Harvey, J., Kozak, R, Lubiniecki, A.., Rubino, M., Schubert, D., Wiebe, M., Woollet, G. 1997. Assessment of Risk of Bovine Spongiform Encephalopathy in Pharmaceutical Products. Pharmaceutical Research and Manufactures of America (PhRMA) - BSE Committee. Technical document, Washington D.C. (USA). 58 pp

BGA (German federal health Office), 1994. BSE and Scrapie - German Federal health Office (BGA) on Safety Measures to be adopted for Medicinal Products. In: Drugs made in Germany, Vol.37 (N°2): pp 36-49.

Brown, P., Wolff, A., Liberski, P.P.,Gajdusek, D.C.,1990. Resistance of scrapie infectivity to steam autoclaving after formaldehyde fixation, and limited survival after ashing at 360°C: practical and theoretical implications. J.Infect.Dis. Vol.161: pp 467-472.

Bruce, M., Chree, A., McDonnell, I., Foster, J., Pearson, G., Fraser, H., 1994. Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier. Philosophical Transactions of the Royal Society

Detlev, R., Kellings K., Post, K., Wille, H., Serban, H., Groth, D., Baldwin, M.A., Prusiner, S.B., 1996. Disruption of Prion Rods Generates 10-nm Spherical Particles Having High ?-Helical Content and Lacking Scrapie Infectivity. Journal of Virology, March 1996, Vol.70. (3):1714-1722

Dickinson, A.G., Outram, G.W., Taylor, D.M., Foster, J.D., 1989. Further evidence that scrapie agent has an independent genome. In: Unconventional virus diseases of the central nervous system. Paris 2-6 December 1986, pp 446-459. Edited by Court, L.A., et al., 1989. Fontenay-aux Roses (France).

Dickinson, A.G., Taylor, D.M., 1978. Resistance of scrapie agent to decontamination. New England Journal of medicine, Vol.299, pp. 1413-1414.

E.C. (European Commission), 1994. Report on detailed procedures for the validation of rendering processes adopted by the Scientific Veterinary Committee (Animal health Section) on 12 December 1994.

E.C. (European Commission), 1996a. The Scientific Veterinary Committee. Opinion of 9 April 1996 on the risk associated with certain animal products in relation to Bovine Spongiform Encephalopathy (BSE).

E.C. (European Commission), 1996b. The Scientific Veterinary Committee. Opinion of 18 April 1996 on the results of the rendering study Phase II - Scrapie.

E.C. (European Commission), 1996c. The Scientific Veterinary Committee. Report on the Control of risks from BSE- and Scrapie-infected material in regard to protection of public and animal health. Adopted on 21 October 1996.

E.C. (European Commission), 1997a. Rapport de la Conférence Scientifique Internationale sur les Farines Animales. Bruxelles, 1 & 2 juillet 1997.

E.C. (European Commission), 1997b. Opinions on the safety of tallow and of tallow derivatives, adopted by the Multidisciplinary Scientific Committee / Scientific Steering Committee on 8 September 1997.

Eleni, C., Di Guardo, G., Agrimi, U., 1997. Encefalopatia Spongiforme Bovina (BSE): Analisi del Rischio in Italia. Large Animals Review, Vol.3 (N°4): pp. 5-15.

EMEA (The European Agency for the Evaluation of Medicinal Products, 1997. Revised draft 14 - rev.1 (2nd September 1997) of the Committee for Proprietary Medicinal Products (CPMP) Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Kimberlin, R.H., 1994. Presentation in: Transmissible spongiform encephalopathies: a consultation with the Scientific Veterinary Committee of the European Communities. Brussels, 14-15 September 1993. Kluwer Academics. Dordrecht, p. 455**.**

Kimberlin R.H., 1996. Bovine spongiform encephalopathy and public health: some problems and solutions in assessing the risks. In: **Court, L. and Dodet, B., Eds., 1996.** Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Proceedings of the IIIrd International Symposium on Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Elsevier, Paris, 16 pages.

Lasmézas, C.I., Deslys, J.-P., Demaimay, R., Adjou, K.T., Hauw, J.-J., Dormont., D., 1996. Strain specific and common pathogenesis events in murine models of scrapie and bovine spongiform encephalopathy. Journal of General Virology, Vol.77: pp 1601-1609.

MAFF (Ministry of Agriculture and Fisheries, UK), IAH (Institute of Animal Health), Prosper De Mulder, CNEVA (France), 1997. Inactivation of the BSE and scrapie agents during the rendering process. Final report of the Study contract N° 8001 CT90 0033 co-funded by the European Commission and MAFF.

OIE (Office International des Epizooties), 1997. Bovine Spongiform Encephalopathy (BSE). Chapter 3.2.13 of the OIE International Zoo-Sanitary Code on BSE.

Prusiner, S.B., 1997. Prion Diseases and the BSE Crisis. Science, Vol. 278 (10 October 1997): pp 245-251.

République Française, 1996. Comité Interministriel sur les Encéphalopathies Subaiguës Spongiformes Transmissibles. Réponses aux questions du Directeur Général de la Santé, du Directeur Général de l'Alimentation et du Directeur Général de la Consommation, de la Concurrence et de la Dépression des Fraudes, adressées au Comité en juillet 1996.

Riedinger, O., 1998. Stellungnahme zum vorläufigen Arbeitspapier der "BSE/TSE-working group", das unter Federführung van Prof.Piva am 12.02.98 in Brüssel beraten soll. Discussion paper. 10pp

Robinson, M.M., Hadlow, W.J., Huff, T.P., Wells, G.A., Dawson, M., Marsh, R.F., Gorham, J.R., 1994. Experimental infection of mink with bovine spongiform encephalopathy. Journal of General Virology, Vol.75, pp.2151-2155.

Taylor, D., 1997. Current science on inactivation of TSE. (Extract from a public presentation). (also attached to COLIPA, 1997).

Taylor, D.M., Fraser, H., McConnell, I., Brown, D.A., Brown, K.L., Lamza, K.A., Smith, G.R.A., 1994. Decontamination studies with the agents of bovine spongiform encephalopathy and scrapie. Arch. of Virol., Vol. 139: pp. 313 - 326.

Taylor, D.M., Woodgate, S.L., Atkinson, M.J., 1995. Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. Veterinary Record, Vol.137: pp.605-610.

Taylor, D.M., Woodgate, S.L., Fleetwood, A.J., Cawthorne, R.J.G., 1997. The effect of rendering procedures on scrapie agent. Veterinary Record. Vol.141, pp. 643-649.

Vanbelle, M., 1997. The scientific aspects of the safety of Meat and Bone Meals: how to ensure food security and that of the animals. Presentation made at the occasion of the International Meat and Bone Meal Conference, Brussels, 1-2 July 1997.

WHO (World health Organisation), 1995. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies. Geneva, 17-19 May 1995. Document WHO/CDS/VPH/95.145

WHO (World health Organisation), 1996. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies.(With the participation of FAO and OIE) Geneva, 2-3 April 1996. Document WHO/EMC/DIS/96.147.

WHO (World health Organisation), 1997. Report of a WHO consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies.(With the participation of the Office International des Epizootie, OIE) Geneva, 24-26 March 1997.

Wilesmith, J.W., Wells, G.A.J., Cranwell, M.P., Ryan, J.B.M., 1988. Bovine spongiform encephalopathy: epidemiological studies. Vet.Rec., Vol.123: pp.638-644.

Wilesmith, J.W., Ryan, J.B., Atkinson M.J., 1991. Bovine spongiform encephalopathy: epidemiological studies on the origin. Vet.Rec., Vol.128, pp.199-203..

Woodgate, S., 1997. TSE Agents: Inactivation by rendering systems and the role of inactivation research on new processing regulations for the European rendering industry. Conference paper. Lipidex 97: 18-21 March 1997 Symposium 1 Tradefair. Antwerp (B). also attached to COLIPA, 1997)

4. On the production of meat and bone meal

In order to express an opinion on the safety of meat and bone meal it is important to consider a number of aspects of the production conditions which may affect the safety of the end product.

4.1 Continuous or batch processing.

On the question which type of production process (batch or continuous) is the safest, it can reasonably be expected that no difference in the effectiveness will occur provided the time/temperature/pressure parameters required for inactivating or eliminating the TSE agent are effectively achieved in every part of a same batch during batch or continuous processes. The problem related to the industrial equipment is to ensure the reaching of the desired temperature in every point of the autoclave for the required time. Available data prove the significant reduction of infectivity only when treating batches at 133°C for 20 minutes and 3 bars of pressure. However, the concern that in operational plants working in continuous the time/temperature/pressure conditions may not necessarily be reached in every point of the bulk, may be a perceived problem, rather than an actual one because the highest-risk tissues (brain and spinal cord) are relatively soft and will tend to break up and disperse onto the surface of the more solid particles. Analytical systems should therefore be developed to monitor or verify that the announced process conditions were really achieved in every part of a same batch in the autoclave, be it processed as a batch or under continuous conditions.

4.2 Meat and bone meal traces in ruminant feeds from cross -contamination

A majority of the enterprises producing feeds produce both monogastric and ruminants concentrates. Since ruminants concentrates are not always produced in dedicated lines, in most cases ruminant concentrates are up to today contaminated with MBM (microscopy evaluation and search of specific bone fragments - lower limit of individuation of 0.01% or less). The problem is not restricted to the production industries, but also to the transport system of raw materials and concentrate for ruminants (most of all concentrate in meal form).

Given the present production systems, a real zero presence level cannot be considered on scientific grounds. The implementation of good manufacturing practice (GMP) in several plants is improving, even though not excluding, the risk of contamination of raw materials. It would therefore be useful to examine the possibility of fixing a maximum level of acceptance of proteins from mammalian material based on the sensitivity of the analytical method or on a precise definition. The risk analysis preliminary to defining tolerance limits should take into account, amongst others:

- the fact that the “133°C / 20 minutes / 3 bar” treatment imposed by the UE is in vigour since 1 April 1997;
- the fact that meat and bone meals are produced only from low risk materials;
- the infectious potential of different extraneural tissues, which may vary according to the animal species;
- the dose needed to infect an animal; etc.

5. Some considerations regarding the safety of meat and bone meal

Regarding the safety of meat and bone meal the working group has made the following considerations:

- The origin of the BSE epidemic in the UK is directly linked to the consumption of meat and bone meal;
- The respect of the conditions of "a maximum particle size 50 mm, a process of 133°C at 3 bars during 20 minutes" do not fully guarantee a totally safe product if the raw material was highly contaminated.
- Apart from the major experiment run in Edinburgh (Taylor et al., 1995; MAFF, 1997; Taylor et al., 1997), the number of other scientific experiments looking into the safety of meat and bone meal (and tallow) with regard to TSEs is, to the knowledge of the Scientific Steering Committee, rather limited if not nihil. Also, the experiment, because of its scope, size and duration, has not been repeated in other laboratories. Finally, the experiments were simulations carried out at a pilot scale and the extrapolation of the results (scaling up) into the real operational industrial conditions may therefore not be automatic. No test results, confirming the hypothesis that meat and bone meal are 100% safe, are available from operational rendering plants. On the other hand, the above pilot-scale experiments were not simply laboratory approximations of rendering processes, but were carried out in actual (although pilot-scale) rendering equipment. In collaboration with the industry it was determined how the pilot-scale equipment could be operated to provide a realistic representation of what occurs in full-scale rendering. Also, most validation studies done on to the safety of a wide variety of biopharmaceutical products with respect to TSE agents, are almost always carried out on scaled down versions of the manufacturing processes that are spiked with TSE agents.
- The mice infection tests which are in most cases carried out to detect TSE infection, may not be (fully) representative for a system of homologous detection between animals of the same species (e.g., from bovine to bovine).The sensitivity of the mouse bioassay for assaying TSE agents from cattle or sheep will be compromised by the species barrier. Cattle-to-cattle transmission of BSE by intracerebral route is known to be about 1.000-fold more effective than cattle-to-mouse transmission by the same route (unpublished data from the UK Central Veterinary Laboratory at Weybridge). Superficially, this might appear to compromise any conclusions drawn from the rendering studies with regard to the safety of meat and bone meal. However, in assessing risks related to the consumption of meat and bone meal, the much greater efficiency of establishing infection in mice by the intracerebral (compared with the oral) route of infection must be considered. For example, the difference in efficiency between these two routes for scrapie in mice is 100.000-fold (Kimberlin, 1996). Also, it has been calculated that the transmission of BSE to mice by the oral route is 200.000-fold less efficient than by intracerebral challenge (Kimberlin, 1994). These data seem to indicate that the negative results from the mouse bioassays of meat and bone meal in BSE and scrapie-spiked rendering studies can be viewed with a considerable amount of confidence with regard to any risk from infection by its consumption. On the other hand, however, certain strains of natural scrapie are transmitted as easy by the peripheral as by the central route and, for example,

the infection of mink by the BSE agent is almost equally effective by the oral route as by the mixed parenteral/intracerebral route (Robinson et al., 1994). The SSC notes that the scientific discussion on the absolute and relative differences in infectivity according to the way of transmission (oral or central) and depending upon the species barrier, is not yet conclusive and is still ongoing.

- Depending upon the strain and the host, it is possible to have differences in incubation times, pathogenesis, distribution of the lesions in the central nervous system, amount of infective PrP^{Res} and its location inside the central nervous system, etc. (e.g., Lasmézas et al., 1996; Kimberlin et al., 1983; Dickinson et al., 1989; Bruce et al., 1994). There are also known differences between some strains of scrapie agent in terms of their thermo-stability (Dickingson and Taylor, 1978; Kimberlin et al., 1983). To date, however, there are no compelling data to indicate that BSE agent is more thermo-stable than scrapie agent.
- The physico-chemical state of the material (size of the particles, state of desiccation, presence of lipids, ...) may affect the heat transfer.

6. The question.

The Working Group therefore addressed the following question:

"Assuming that meat and bone meal is only used as an animal feed, should the production processes respecting these conditions of "133°C / 3 bar / 20 minutes", and as long as no other processes have been validated or accepted, necessarily be combined with the respect of conditions regarding the origin of the animals (geographical and animal sourcing), the nature of the materials (specified risk materials) and the age of the animals?"

7. Scientific opinion

Preliminary notes:

a) In its opinion of 22-23 January 1998 defining the BSE risk for specific geographical areas, the Scientific Steering Committee has listed the factors contributing to the incident and propagation risks in a geographical area. This list is attached as an annex, for ease of reference. More work needs to be done on the definition of risk regions or countries. The Committee is preparing a further opinion on the geographical aspects of BSE risks.
The four classes of the geographical aspect of BSE risks used in the opinion hereafter, are therefore indicative and, for the time being, are: "high risk countries", "lower risk countries", "countries considered free of BSE or classified as at negligible risk" and "Countries with an unknown TSE status". The corresponding wording of the opinion hereafter may thus possibly have to be revised / updated in accordance with the forthcoming Scientific Steering Committee opinion on the geographical aspects of TSE/BSE risks and on the criteria to be applied for the evaluation of the TSE status of a country.

b) Notwithstanding the fact that the question put to it refers to the safety of meat and bone meal from mammalian animals, the Scientific Steering Committee the opinion below only covers MBM derived from ruminants possibly infected with BSE or scrapie.

c) The opinion hereafter does not address the issue of the intr insic risks related to the practice of feeding back of animal derived feedingstuffs to the same or similar species.

The Scientific Steering Committee adopted the following opinion on the safety of meat and bone meal:

1. Definitions:

- *For the purpose of the present opinion meat and bone meal derived from mammalian animals are defined as processed animal protein intended for animal consumption which has been treated so as to render it suitable for direct use as a feeding stuff or as an ingredient in a feeding stuff for animals. Rendering means any processing of slaughter by-products, animals unfit for human consumption or meat scraps for the production of meat and bone meal. The term includes the collection of such materials and subject them to minimal processing, or distribute them to firms other than renderers whose intended use for the products may include animal feed. The term includes also blending animal protein products.*
- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem, inspection and that are certified and identifiable as fit for human consumption on the basis of the existing national and EU legislation. The Scientific Steering Committee stresses that positive identification of material not fit for human consumption should be possible, to avoid possible entering of such material in the food or feed chains.*
- *Unless otherwise specified, the wordings "SRMs or Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.*
- *The wording "133°C/20'/3 bars" refers to production process conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. Regarding the fact whether they should be realised under batch or continuous conditions, the Scientific Steering Committee is of the opinion that there will be no difference in the effectiveness provided the time/temperature/pressure parameters are effectively achieved in every part of the material being processed. These conditions are expected to be realised for non desiccated raw material with a particle size of maximum 50mm and with a lipid and water content that normally can be expected for animal tissues and where this water generates the steam during the rendering process or, alternatively, where the starting material is drier but where steam was injected in the beginning of the production process so that the preceding normal conditions are realised. If the initial conditions of the starting material are different, then the required temperature/time/pressure combination may have to be adjusted accordingly. . Equivalent processes should be evaluated and acknowledged on a case by case basis.*

2. *Concerning the raw material it has to be accepted that, as long as no test is available which allows to diagnose non-clinical BSE or scrapie cases (pre-mortem), the only way of determining that the basic raw material is of negligible risk, is a procedure of sourcing of the raw material.*

3. *The Scientific Steering Committee strongly recommends that manufacturers implement and respect HACCP[20] procedures. It is essential to identify and describe the hazards and critical points for the different processes utilised in production. Two of these points is certainly the traceability and treatment at the origin (e.g., removal of specified risk materials) of the raw material.*

4. *The sections of the opinion hereafter cover the approach to be followed if the risk of infectivity of meat and bone meal is to be reduced to the lowest possible level. In addition a more detailed risk analysis could be carried out to assess the exact level of the risk of infectivity for an animal. Such risk assessment would depend upon:*

   - *type of final product and infectivity reduction capacity of the production procedure;*
   - *the geographical origin of the raw material;*
   - *the type of raw material, including the age of the animals;*
   - *the removal or not of specified risk materials;*
   - *the incidence and propagation components of the BSE borne risk, as specified in the opinion of 22-23 January 1998 of the Scientific Steering Committee, defining the BSE risk for specified geographical areas*

   This assessment requires results of experiments on and justified estimates of reduction factors during the various steps of the production process, from sourcing to marketing. Such data are not always available, as some experiments are still ongoing or only in a planning phase. The Scientific Steering Committee intends to undertake this risks assessment exercise in collaboration with recognised experts and institutions.

5. ***Further criteria to be met in order to ensure a degree of safety of meat and bone meal from mammalian origin allowing it to be fed to non-ruminants.***

   5.1. *<u>For countries considered to be 'BSE free or classified as at negligible risk'</u>:*

   Whether or not the source of the raw material can be 'considered free of a given TSE' must be the object of detailed evaluation by the appropriate independent expert bodies; as long as no tests are available which allow to diagnose non-clinical TSE cases (pre-mortem), the only way of determining that the basic raw material is of negligible risk, is if the TSE-free status of the origin of the material was evaluated on the basis of an appropriate procedure using recognised criteria. Raw material from such a source, satisfying the previous conditions can be used without additional conditions regarding minimal production processes or removal of specified risk materials, provided it is also fit for human consumption. Nevertheless, the Scientific Steering Committee recommneds, as an additional precautionary measure to prevent also for these countries the possible building up of circulating TSE-agents as a result of sporadic

[20] Hazard Analysis and Critical Control Points

spontaneous cases, the submission of the material to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents.

5.2. <u>For lower risk countries</u>:

The raw material has to originate from animals certified officially to be fit for human consumption. The material should be submitted to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. However, it cannot be excluded that under worst case conditions, traces of infectivity could remain. In order to minimise a possibly remaining risk of infectivity, specified risk materials shall be excluded from the production of meat and bone meal and other animal feed.

The SSC further recommends that measures are taken to avoid cross contamination between raw material from different animal species and between the final products to be consumed by different species.

The Scientific Steering Committee recognises that the fact of combining both the requirements of using animals that are fit for human consumption and of submitting the material to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents, may be perceived as too precautionary. Accepting that this combination of conditions should not necessarily become a general principle, the SSC nevertheless is of the opinion that reaching the maximum possible level of safety should be the objective, in order to prevent a possible build up of circulating TSE-agents in animals as a result of sporadic outbreaks of TSE that may occur. Whilst an additional submission to 133°C during 20 minutes at 3 bar of material already declared fit for human consumption and to be used as human food cannot realistically be envisaged, the manufacturing of meat and bone meal for animal consumption does accept such conditions. As the TSE transmission barrier between animals of a same species is lower than between animals used as food and humans, to prevent also for these countries the possible building up of circulating TSE-agents as a result of sporadic spontaneous cases and more generally, because of the risk of microbiological contamination in rendering and processing plants, this combination of conditions increases the safety of the animal as human food.

5.3. <u>For high risk countries</u>:

As it cannot be excluded that under worst case conditions, traces of infectivity could remain despite of the all the possible safeguards put into place, the Scientific Steering Committee recommends that no meat and bone meal, to be used as feed for mammalian animals, should be produced from ruminant animals.

Note:

The Scientific Steering Committee considered but eventually rejected the following alternative option:

The raw material has to originate from animals certified to be fit for human consumption. The specified risk materials shall be excluded from the production of meat and bone meal and other animal feed. The material should be submitted to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. (However, under these process conditions, it cannot be excluded that under worst case conditions, traces of infectivity could remain.) The material should be sourced from animals that are young enough not to represent any realistic risk of harbouring BSE or scrapie infectivity at detectable levels. Dedicated rendering plants and transports should be used, to avoid cross-contamination between raw material from different animal species and between the final products to be consumed by different species.
The above alternative was rejected because it was considered as not being realistic for practical reasons and because of the difficulties that would be encountered when monitoring and enforcing its implementation. However, the second alternative could be considered as an intermediate step for high risk countries but where the BSE epidemic is under control and which are in the process of becoming (lower) risk countries.

5.4. *Countries with an unknown TSE status should be evaluated individually on the basis of a detailed evaluation using appropriate criteria As long as its status remains unknown, a region or country is considered as a high risk one.*

6. *On the question whether the above specified production process conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents, should be realised under batch or continuous conditions, the Scientific Steering Committee is of the opinion that there will be no difference in the effectiveness provided the time/temperature/pressure parameters are effectively achieved in every part of the material being processed. The SSC further recommends that analytical systems are developed to monitor or verify that the announced process conditions were really achieved in every part of a same batch in the autoclave, be it processed as a batch or under continuous conditions.*

7. *The Scientific Steering Committee finally stresses the urgent need of a study and risk analysis being carried out so as to possibly define acceptable tolerance limits of the possible content of impurities and proteins from mammalian material in feeds which theoretically should not contain any such impurity. A zero contamination level is indeed difficult -if not impossible- to achieve, also from a scientific point of view. To determine the content of impurities and proteins, an accepted standard analysis method would also be required."*

Summary table: criteria to be met in order to ensure a degree of safety of meat and bone meal from mammalian origin allowing it to be fed to non-ruminants.

Geographical origin of the animals:	Criteria to be met:
BSE FREE or NEGLIGIBLE	- Material certified as being from area considered BSE free or at negligible risk. - Certified as fit for human consumption. - Production process respecting 133°C/20'/3 bars or equivalent in terms of inactivating/eliminating the BSE or scrapie agent; batch or continuous process.
LOWER RISK	- Certified as fit for human consumption [21]. - Specified risk materials [22] excluded. - Production process respecting 133°C/20'/3 bars or equivalent in terms of inactivating/eliminating the BSE or scrapie agent; batch or continuous process. - Measures to avoid cross-contamination.
HIGH RISK	– No meat and bone meal, to be used as feed for mammalian animals, should be produced from ruminant animals.
STATUS UNKNOWN	To be evaluated; if no judgement possible: consider as high risk

[21] Fit for human consumption means here that the animal should comply with all the appropriate and relevant national and EU legislation.

[22] The wording "SRMs or Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.

Annex E to the SSC Opinion of 19-20 February 1998.

Opinion on the revised version of the UK Date Based Export Scheme and the UK proposal on compulsory slaughter of the offspring of BSE-cases, submitted on 27.01.98 by the UK Government to the European Commission

Adopted by the Scientific Steering Committee at its plenary meeting of 19-20 February 1998.

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Opinion on the revised version of the UK Date Based Export Scheme and the UK proposal on compulsory slaughter of the offspring of BSE-cases, submitted on 27.01.98 by the UK Government to the European Commission

Adopted by the Scientific Steering Committee at its plenary meeting of 19-20 February 1998.

Background:

The SSC at its plenary sessions of 8-9 December 1997 and 22-23 January 1998 adopted a report on a UK proposal on a Date Based Export Scheme. The proposal was submitted on 2.10.97. As a reaction to this report, a revised version was submitted on 27 January 1998. This new version responds to the suggestions and questions made by the SSC.

Comments

The SSC has the following comments on the revised proposal:

In the revised version most suggestions and recommendations made by the SSC have been commented on and answers are provided. However, the UK expressed to be unwilling to introduce a strict obligation on the farmer to keep a dam alive and traceable for six months after birth. This was recommended by the SSC both for the date based export scheme and for the proposal on compulsory slaughter of the offspring of BSE cases. This would improve the detection of calves born to dams developing BSE during this period and thus reduce the possible risk of maternal transmission.

The revised proposal also contains an assessment of the risk that maternally infected cattle enter the food chain. The results show that under a worst case scenario (the details are given in the proposal), the risk of an undetected BSE case in the last six months of the incubation period being slaughtered for food is equal to 2 per 100.000 (or 46 animals in 1998) and this risk is diminishing every subsequent year. The UK concludes that this risk is so low that it does not justify the need for any additional control. If additional controls should nevertheless be required by the EC, the UK suggest that producers are obliged to provide a legally binding declaration and corresponding evidence that the dam of the animal was alive six months after its birth at the time of slaughter.

The SSC is of the opinion that the maternal risk for BSE infectivity should be kept at the lowest possible level. The Scientific Steering Committee also finds that the obligation to farmers proposed by the UK, offers an equal risk reduction for BSE infectivity in exported de-boned meat as the requirement recommended by the SSC in its report of 8-9 December 1997. It therefore leaves it to the EC to decide – taking into account the practicalities and costs involved- which measure it will request from the UK: a legally binding declaration by the farmer or a firm decision from the UK authorities that the dams will be kept alive and traceable for 6 months.

The proposal for compulsory slaughter of offspring of BSE cases still only involves the first generation animals. The evaluation requested by the SSC on possible maternal risk for BSE in the whole descendant maternal line should be presented to the European Commission before a final decision is taken whether the whole or only part of the maternal line to BSE cases should be culled.

With respect to the proposed plan for eradication of BSE, the Scientific Steering Committee recommends that the evaluation of the consequences of not culling the offspring of BSE cases born before 1 August 1996, should also be presented before an amendment of the eradication plan is decided upon.
