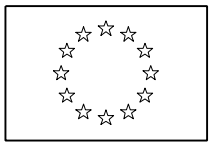

SCIENTIFIC REPORT AND OPINION ON

THE SAFETY OF GELATINE

UPDATED BY

THE SCIENTIFIC STEERING COMMITTEE

AT ITS MEETING OF 20-21 JANUARY 2000

(The corresponding sections are underlined with dots)

I. REPORT ON THE SAFETY OF GELATINE

1. Definition

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

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 matrices 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 mandate of the Scientific Steering Committee was 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 that 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 kind 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 out 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 138-140°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 procedure 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, 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 (EMEA) 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/or 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 Multidisciplinary Scientific Committee (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 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 TSEs (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 CPMP 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 exporting to the 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 the vertebral column of cattle, sheep and goats of over 12 months of age for 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*

immunocytological 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 that BSE is increasingly being revealed as having a tissue based infectivity which seems similar to that of scrapie.[1]

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,infectivity of the bone marrow of naturally infected bovines has, to present knowledge, not been detected. According to Hadlow et al. (1982), infectivity has been reported in bone marrow of Suffolk sheep with natural, clinical scrapie but (Hadlow et al., 1980) not in goats with natural scrapie.

4. 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.

4.1 The production of gelatine (see G.M.E., 1997a,b,c; 1998)

Gelatine 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.

4.1.1 The acid-alkaline process

A typical 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 producesa

1 [Footnote inserted at the SSC meeting of 20-21 January 2000:] However, up to 20 January 2000, no infectivity has been detected in the lymphoreticular tissues of natural cases of BSE, even by intracerebral injection of cattle. In contrast, spleen and lymph nodes inscrapie-infected sheep appear to be almost universally infected.

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. ($Ca(OH)_2$, pH = 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 may be 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 aprecise 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 138 - 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) safe 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 countries with higher than negligible BSE risk and if they exclude hides from cattle that have signs of neurological disease

4.1.2 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 theosseine is soaked overnight at pH below 4.

4.1.3 The heat/pressure/time process

A process which is currently applied by the industry for the production of gelatine can be summarised as follows:

- Finely crushed bone chips are degreased with hot water (85-90°C, pH = approximately 5, during an average of 15 minutes);
- After centrifugation and pre-drying, the bone chips are dried (rotating drier) in a stream of hot air (over 400°C) and then calibrated (mean particle size 15-20 mm);
- The calibrated bone chips are first pre-heated with steam (115°C, 1.7 bars, 10 minutes) in an autoclave;
- The pre-heated bone chips are autoclaved and pressurised with steam at 133°C, 3 bars, 23 minutes and then after depressurisation the gelatine is extracted with water; (10°C in most steps, 20 minutes);
- The steam heating (133°C/3bars/20 minutes) and water extraction is repeated eight times on the residual bone chips;

The gelatine extraction yield is decreased after each step. To obtain sufficient concentration during the last 4 heatings, the extraction is realised with the gelatine liquid obtained in previous extraction steps.

- The extractions are finally purified by filtration, centrifugation and are sterilised during 5 seconds at least 148°C.

The issue of the safety of such process with respect to possible residual TSE infectivity should thus also be addressed.

4.1.4. An alternative, continuous process for the production of gelatine

In June 1998, the Scientific Steering Committee was requested to evaluation of an alternative process for the production of gelatine regarding its equivalency with commonly used industrial gelatine production processes in terms of its capacity of inactivating/eliminating possible TSE infectivity in the raw material.

The production process is a very rapid continuous one and, includes steps such as:

defattening, grinding, an acidulation and acid extraction steps, filtration, cooling, ultrafiltration, concentration and de-ashing, sterilisation and drying.

Here also, the issue of the safety of such process with respect to possible residual TSE infectivity should be addressed.

5. Some considerations regarding the safety of gelatine

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

5.1 The opinion of the association Gelatine Manufacturers of Europe (GME) 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 tons gelatine produced: 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 of Gelatine Manufactures of Europe (GME), which represents most of the EU's gelatine producers, all of their associated gelatine-manufacturing sites in the European Union are certified according to ISO 9000 international standards. The GME's gelatine manufacturers claim to respect the following sanitary guarantees, which are also recommended in OIE documents: 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 veterinary services; they come from animals recognised as suitable for human consumption. For each gelatine lot (even

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

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 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.

5.2 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."*

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3 HACCP: Hazard Analysis Critical Control Points

5.3 The US FDA's opinion and proposal

The opinion of the FDA is based on the preliminary data presented in 1994 by the gelatine industry in relation to the BSE transmission routes and excludes from 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.

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 skin 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 intended for animal use are banned by the USDA/APHIS (United States Department of Agriculture / Animal and Plant Health Inspection Service) in the US if they come from BSE countries.

5.4 Other sources of information on the safety of gelatine

5.4.1 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.

5.4.2. 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

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

5 GFAP stays for glial fibrillary acid protein.

(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.

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 injected 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.

5.4.3. Gelatine manufacturers validation studies.

a. With respect to the possible BSE transmission through gelatine, the *Gelatine Manufacturers of Europe* (GME) took the initiative for a validation study on the removal/inactivation capacity of a typical gelatine manufacturing process, assumed to be the most stringent one in terms of possible reduction of TSE infectivity (Inveresk Research International, 1998b).

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

   The material used consisted of scrapie infected mouse brain ($\log_{10}$ ID_{50}=7.44) for the acid treatment and $\log_{10}$ ID_{50}= 7.90 for the liming treatment. This material was inoculated intracerebraly to susceptible mice to calculate the reduction factors of infectivity in the two respective steps 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 1.17 $\log_{10}$ (approx. 10 fold).

   The liming treatments after 20 days, 45 days and 60 days, gave also partial reduction of potential infectivity of respectively 2.33 $\log_{10}$, 2.23 $\log_{10}$ and 2.10 $\log_{10}$. The level of reduction is not increased as the length of treatment is extended and seems not to be associated linearly with the length of incubation.

   In an the additional stage of the above Validation study of the clearance of scrapie from the manufacturing process of gelatine (Inveresk Research International, 1998c), a combined chemical treatment (acid treatment and lime treatment) was selected and artificially challenged with high titre scrapie agent ME7 (titre: $\log_{10}$ ID_{50}= 7.90). The results show that, 18 months after inoculation, the reduction factor was 2.84 $\log_{10}$. If both processes were fully additive, then the reduction factor should have been 3.40 $\log_{10}$.

b. The alkali-treatment step is a critical step in the overall manufacturing process. Sodium hydroxide is used in many areas of the gelatine industry as an alternative to the use of lime as an alkali treatment agent. The results of a validation study to show the reduction of scrapie agent by a NaOH treatment has been made available by the company Goodman Fielder Ingredients Ltd. (Shepherd, 1999). As in the previously mentioned Inveresk studies, the material used consisted of scrapie infected mouse brain (log_{10} ID_{50} = 7.8). This material was inoculated intracerebraly to susceptible mice to calculate the reduction factors of infectivity. The two soda alkali treatments (0.25 M. NaOH during 5 days at 15°C ± 2 and 0.30 M. NaOH during 7 days at 15°C ± 2) gave partial reduction of potential infectivity (after 18 months inoculation) of respectively 4.82 log_{10} and 5.25 log_{10}. Without the test material over 2 log_{10} of infectivity was detected following each treatment, indicating that no significant difference in scrapie infectivity was influenced by the change in concentration of NaOH and the length of incubation validation. It is clear that sodium hydroxide is more effective than calcium hydroxide , even when its molarity is around half that of calcium hydroxide. At about the same pH (13.4 versus 12.5) the inactivation power is at least 2 log_{10} higher for sodium hydroxide than for calcium hydroxide after a treatment of 5 to 7 days at room temperature.

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

e. 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 one thousand billion patients treated for one year as a result of pharmaceutical use of gelatine, under the conditions of sourcing and processing indicated in the report as an example)

The SSC is concerned of the fact that, according to GME (GME,1998c; INVERESK, 1998b; Shepherd, 1999), the material used for the validation studies on the removal or inactivation capacity of the TSE agent did not consist of spiked bones but of scrapie infected brains, which are two different environments. However, for a final assessment to be made, a inactivation experiments should be carried out on spiked bone material. The SSC recommends that research on the elimination and inactivation of TSE, including BSE, agents during the gelatine manufacturing process should also be carried out on raw material really used for gelatine production and 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.

5.5 The *"133°/20'/3 bars heat/pressure/time conditions"* for the production of gelatine regarding its equivalency with the acid-alkaline process in terms of its capacity of inactivating/eliminating possible TSE infectivity in the raw material.

The bone material used for this particular preparation may potentially be cross-contaminated with (dried) brain, spinal cord and bone marrow[6].

It has been reported that it becomes more difficult to inactivate scrapie-infected brain-tissue by heat after it has been dried (Asher et al, 1986; 1987). However, it seems (Gelatine Delft, 1998) that the degreasing step, which precedes the drying of the bones, and carried out at a pilot scale which represent the commercial degreasing process under laboratory conditions[7], reduces the brain protein levels by a factor 300-800. It may be expected that, under operational conditions, this reduction is higher because the same laboratory experiments at pilot scale resulted in degreased bone with a fat content of 6%, compared with 3% in the commercial process.

The Working Group considers that the extrapolation of data on inactivation/reduction of the TSE agent during the process of rendering animal waste into meat-and-bone meal, to a similar heat treatment of bones can not be done automatically with a high degree of certainty. This means, that if the question has to be answered indetail, experiments using as exact conditions as possible should be performed. Otherwise one has to extrapolate several parameters, including the effects of water content[8], lipid content, particle size, heat penetration and so forth. These parameters may have both a stabilising and destabilising effect on the stability of the agent and may change the temperature or time settings of the treatment.

The experiments on which the reduction factor for 133C/20min/3bar is based, involves treatment for MBM production of raw material with a certain average composition and water content. If the raw material exclusively bone material (which may previously have been dried), heat penetration may be changed. (Thus a longer pre-heating phase or heating time may be required.) The water content may not be adequate for efficient inactivation.

During the common production process of meat-and-bone meal from fresh material, the steam is generated by the water naturally present in the tissues. The water content during such process is estimated at approximately 60%. The maximum water content of bones is about 25-30%.

Although dried bone chips have a water content of only around 10%, it is evident that they become hydrated during the manufacturing process. Gelatine could not be extracted unless

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6 Results of the now completed BSE pathogenesis experiment in cattle (Wells et al, 1998) have shown that tests in mice for infectivity of bone marrow were positive only in the group killed at 38 months after infection with BSE, when clinical disease was evident in the cattle, and not at an earlier (2 to 36 months) or later (40 months) time after exposure to BSE (Wells *et al*, 1999). The current SEAC conclusion (SEAC, 1998) is that *"the positive result at 38 months cannot be discounted and may indicate that infectivity in bone marrow occurs occasionally, when clinical signs are apparent and there are already very high levels of infectivity in the central nervous system.*" It is noted that BSE infectivity in bovine bone-marrow has been detected in only one still ongoing experiment, and only after the onset of clinical signs. Further studies of the infectivity of bone marrow at different time points in the pathogenesis experiment in cattle are being conducted by thei/c challenge of calves. There are no results as yet (Wells, unpublished observations, January 2000).

7 Ten grams of pig-brain thoroughly mixed with 1 kg of bone-chips typically used by gelatine manufactures (average particle size: 12 mm, maximum: 20 mm).

8 For example, for meat-and-bone meal the water content is approximately 60%.

the bone material has at this stage a sufficiently high water content. (According to GSB, 1998, the water content is approx.25% after the pre-heating step and approx. 50% after the first heat and pressure treatment). This means that there is little doubt that steam could be generated and that heat penetration into the 15-20 mm bone chips during the 133°C steam process does occur.

Therefore, whilst awaiting results from TSE inactivation experiments, the Working Group considers that the 133C/20min/3bar conditions, if applied with all relevant parameters listed in the Updated Scientific Report presented on 24-25 September to the Scientific Steering Committee on the safety of meat and bone meal derived from mammalian animals fed to non-ruminant food-producing farm animals (e.g., maximum particle size, enough water and saturated steam[9], core temperature reached in all parts of the material for at least 20 min[10], etc.), would result in a reduction of potential BSE infectivity which is close to or equivalent to the reduction realised during the production process of meat-and-bone meal from a fresh mixture of materials containing bones, meat and other animal offals. According to the SSC opinion of 26-27 March 1998, this process is accepted to result in an infectivity reduction of at least 3 $\log_{10}$, whereas the reduction of the acidulation + liming process of the typical gelatine production process is approx 2.84 $\log_{10}$. (INVERESK Research, 1998).

5.6. The alternative, rapid, continuous process for the production of gelatine

The process description which was made available to the Working Group refers to a pilot production line and at the time being details of the process are missing at an industrial scale. The Working Group notes that not sufficient information was made available on the inactivation capacity of the alternative process. It was therefore impossible to assess its effectiveness in terms of inactivating/eliminating possible TSE infectivity by comparison with the documented TSE infectivity clearances obtained during the various steps of the most commonly used traditional production processes.

[9] Dry saturated steam has a relative humidity of 100%, and is free of moisture droplets carried in suspension.

[10] The working group wishes to stress that this period of 20 minutes should be continuous, without interruptions.

II. THE OPINION

6. 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?"

7. Scientific opinion

7.1 Preamble

7.1.1. The present opinion covers 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 take account of:

- the 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. In order to provide the Commission with two alternative choices, the Scientific Steering Committee will eventually complete the in this opinion followed approach to reduce the risk of infectivity in the final product to the lowest possible level with a quantitative risk analysis. The results of the latter analysis may eventually change or ask for an update of the recommendations hereafter.

7.1.2. 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. On 20 February 1998 the SSC adopted that list, slightly amended, as final opinion. 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.

The Scientific Steering Committee is presently developing a methodology for the geographical risk assessment.

On the basis of the report of the working group, approved by the TSE/BSE ad hoc group, the Scientific Steering Committee adopted on 26-27 March 1998 the following final opinion on the safety of gelatine:

"7.2. 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 mainly from bovines and/or pigs after successive treatments: degreasing, acid treatment, and/or alkaline treatment (liming), washing, filtration, ion exchange and sterilisation.*
- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem inspection and that are certified by a competent veterinary authority 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.*
- *"Healthy animals" are defined as animals which have undergone an ante mortem inspection by an official veterinarian where it was determined that the animals were not suffering from a disease which is communicable to man and animals and that they do not show symptoms or are in a general condition such as to indicate that such disease may occur and they show no symptoms of disease or of a disorder of their general conditions which is likely to make their meat unfit for human consumption. (Definition as given in Directive 64/433/EEC, laying down the rules for ante mortem inspection).*
- *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 and amended on 22-23 January 1998. 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.*
- *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 country or region with a non negligible BSE risk, if a number of criteria are being met which exclude the possible risk of infectivity: 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 be processed in dedicated production lines, but these could be lines used previously for more general purposes provided that there is a sufficient "clean-out" before the start of a dedicated production run.

REGARDING THE ACID-ALKALINE PROCESS:

Definition:

- *"Appropriate production processes" in the sections hereafter refer to processing bone materials and are those processes which have an appropriate efficacy in terms of eliminating TSE agents. For the transformation of bones sourced from countries or regions where the BSE risk is not negligible or zero or where the BSE status is unknown, only those processes are "appropriate" with the highest possible efficacy to eliminating TSE agents. An example of an appropriate production process is: bones finely crushed and degreased with hot water and treated with dilute hydrochloric acid (at a maximum concentration of 4% and pH <1.5) over a period of at least two days, followed by an alkaline treatment of saturated lime solution (pH >12.5) for a period of 20 to 50 days with a sterilisation step of 138-140°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.*

  *Alternative methods with demonstrated equivalent efficacy in terms of eliminating TSE agents may be acceptable. For example, in stead of the liming **step**, a 0.25 - 0.30 molar NaOH treatment during 5-7 days at 15 °C ± 2° seems about 2 log_{10} more efficient. Other methods must be evaluated and acknowledged on a case by case basis, also against the BSE status of the source region or country and the type of material used. (See also item 7.16 of this opinion). For bones coming from high or low risk countries, the liming or (above) NaOH step should always be included.*

  The Scientific Steering Committee calls for the results of the research on the TSE agent inactivation during the manufacturing of gelatine to be made urgently available, in order to possibly revise or broaden the above definition of appropriate production processes.

7.3. Because of existing evidence of the possible presence of remaining impurities,

and given the fact that the number of critical points[11] in the whole production chain is quite large and that their monitoring may not always be easy and evident,

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

7.4. The Scientific Steering Committee strongly recommends that gelatine manufacturers implement and respect HACCP[12] procedures. It is essential to identify and describe hazards and critical points for the different processes utilised in gelatine production.

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

12 Hazard Analysis and Critical Control Points

Two of these points are the traceability and treatment at origin (e.g. removal of specified risk materials) of the raw material.

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

7.6. 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.

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

7.8. The end use of gelatine is human consumption as well as cosmetic product:

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

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

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

Specified risk materials should first be removed to minimise the risks of possible contamination. The origin of the bovine raw materials should be certified to be exclusively from animals that are fit for human consumption (bones) or from healthy animals (hides and skins).

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

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 healthy animals. However, in certain circumstances, the risk profile can be changed, e.g. on the basis of age of the animals, the origin (source herd) 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. As an application of the latter principle, and according to the SSC opinion of 22-23.10.98 on The Safety of Bones Produced as a By-product of the Date Based Export Scheme, bones (except skull and vertebral column) from animals that comply with the conditions set out in the UK Date Based Export Scheme, can be used. The criteria for use should comply with the criteria set out in the above section 7.8.2 for lower risk countries and in the annex to the opinion of 22-23.10.98.

Material from pigs can be used, provided that the animals are certified as fit for human consumption (bones) or healthy (skins) and processed on separate lines in slaughterhouses.

7.8.4. <u>Countries with an unknown BSE status</u> should be evaluated individually on the basis of a detailed evaluation using appropriate criteria. If no judgement on the basis of

available evidence or because of a lack of information is possible, they should be considered as high risk countries.

Remark: The previous statement does not prejudge the opinion of the SSC on the TSE/BSE status of any country. Work on geographical risk assessment is ongoing.

7.9. 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.

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

The same conditions as for food and cosmetic use set out in paragraph 7.8 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.

7.9.2. 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 7.8 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.

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

Where the end products, for which gelatine is needed during 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 7.9. (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 large numbers of healthy subjects for preventive purposes and therefore should carry a minimal risk.)

7.11. 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 paragraph 7.8.

REGARDING THE EQUIVALENCY OF THE "133°/20'/3 BARS HEAT/PRESSURE/TIME CONDITIONS" WITH ACID-ALKALI PRODUCTION PROCESS IN TERMS OF ITS CAPACITY OF INACTIVATING/ELIMINATING POSSIBLE TSE INFECTIVITY IN THE RAW MATERIAL.

7.12 .The Scientific Steering Committee addressed the following question:

"Is a treatment of all ruminant bone material which is not derived from animals born, reared and slaughtered in countries recognised BSE free or at negligible risk, to heating to at least 133°C throughout its substance for a minimum of 20 minutes at a pressure of three bars, with a particle size prior to processing of not more than 50 millimetres and complying with the updated report on MBM regarding the steam requirement without air trapped,

an acceptable alternative to the production conditions laid down in the opinion on the safety of gelatine, namely:

a process which ensures that all bone material is finely crushed and degreased with hot water and treated with dilute hydrochloric acid (at minimum concentration of 4% and pH<1.5) over a period of at least two days, followed by an alkaline treatment of saturated lime solution (pH>12.5) for a period of at least 20 days with a sterilisation step of 138-140°C during 4 seconds".

7.13. The SSC recognised that it becomes more difficult to inactivate scrapie-infected brain-tissue by heat after it has been dried, that the raw material used for the production of meat-and-bone meal and for gelatine has a different composition (e.g., water, fat and protein content) and different physical characteristics and that there may be different heat transfer and inactivation conditions during production. In general, there is an uncertain comparability of "133°/20'/3 bars" heat/pressure/time conditions during the processing of fresh animal waste into meat-and-bone and (fresh or dried) bone material into gelatine.

In the absence of a scientific and comprehensive report on or the results of a validation study on the TSE infectivity inactivating capacity of such processing conditions and the intended end-use of the produced gelatine being for human (and possibly animal) consumption, the uncertainties about the residual risk should therefore be reduced to the minimum possible.

The SSC is also concerned that an acceptance of the equivalent inactivation of TSE infectivity in the present process for the production of gelatine with the process described in the SSC opinion of 26-27 March 1998 may trigger the submission for approval of a number of other production processes for which no validation has been carried out.

Given these concerns, the SSC cannot conclude that "133°/20'/3 bars" heat/pressure/time conditions as described in the report of the Working Group would result in an equivalent safe product compared with the acid-alkaline industrial gelatine production process described in its opinion on the Safety of Gelatine of 26-27 March 1998.

Therefore, for gelatine derived from ruminant bones, the Scientific Steering Committee's Opinion on the Safety of Gelatine adopted on 26-27 March 1998 and updated on 3 April 1998, remains valid. At present, the only preliminary conclusion can be that ruminant bones from animals certified fit for human consumption, to be

used for production of gelatine with heat / pressure / time system, will have to come from BSE-free or BSE-negligible risk countries.

7.14. The industry is invited to organise an independent experiment showing that the series of successive "133°C/20'/ 3 bars" steps for the production of gelatine, results in a BSE infectivity reduction which is at least equivalent to the reduction obtained during the "133°C/20'/3 bars" production process defined in the SSC opinion of 26-27 March 1998 and in the Updated Scientific Report of 24-25 September 1998 on the safety of meat-and-bone meal and which accept an infectivity reduction of at least 3 log_{10}. These experiments should be carried out under conditions similar to the ones in the real industrial processes. The inactivation should be assessed at least for the series as a whole of successive "133°C/20'/ 3 bars" steps and preferably also for the production process as a whole. The data should clearly show that also dry contaminated material can be reduced in infectivity.

REGARDING THE EQUIVALENCY OF AN ALTERNATIVE, CONTINUOUS PROCESS WITH THE ACID-ALKALI PRODUCTION PROCESS IN TERMS OF ITS CAPACITY OF INACTIVATING/ELIMINATING POSSIBLE TSE INFECTIVITY IN THE RAW MATERIAL.

7.15. The SSC considers it impossible evaluate at present the equivalency of the alternative production process described in the attached report of the working group, in terms of the inactivation/elimination of TSE infectivity.

As for the classical acid alkaline and for the heat/pressure/time processes, a study with spiked BSE infected raw material is needed in order to estimate the infectivity reduction factor of the production process. The Scientific Steering Committee invites the industry to organise an independent experiment on the TSE inactivation/elimination capacity of the alternative process.

At present, the only preliminary conclusion can be that ruminant bones from animals certified fit for human consumption, to be used for production of gelatine with the alternative system, will have to come from BSE-free or BSE-negligible risk countries.

REGARDING THE EVALUATION ON A CASE BY-CASE BASIS OF ALTERNATIVE PRODUCTION PROCESSES.

7.16 The SSC wishes to propose that any future request for the evaluation of production processes in terms of their equivalency in TSE infectivity inactivation/elimination with other already documented and validated processes, should be accompanied with the results of a validation study and/or a supporting report on the TSE inactivation/elimination capacity of the process.

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

END USE:	Human consumption and cosmetic products	Registered pharmaceutical products and parenteral use Oral or topological	 Parenteral, ophthalmic; implantable product	 As acomponent in manufacture	Industrial use
BSE FREE or NEGLIGIBLE RISK	- animals fit for human consumptio (bones) or healthy (hides); - appropr. Product. process[13]	- As for Human consumption and cosmetic products; - Special grade gelatine if	- As for Human consumption and cosmetic products; - Special grade gelatine if applied to large areas of damaged skin or	- Manufacture of products for parenteral or ophthalmic use or for vaccines: as for	- Appropriate production process[13].
LOWER RISK	- as above AND - SRMs[14] excluded	applied to large areas of damaged skin or to open wounds; - Regulatory licensing[15]	to open wounds; - if bovine material used it should be of negligible risk; - Appropriate and validated purification process; - Regulatory licensing [10] - Dedicated product. lines;	implantable products	- Appropriate production process[13];
HIGH RISK	- Excl. all ruminant materials, except hides from healthy animals;[16] - Pig materials to be processed on separate lines. - Appropr. product. process[13]				- Appr. production process[13]; - Appropriate protection of workers. - If ingestion or exposure risk: as for human use;
Status unknown	To be evaluated; if no judgement on the basis of available evidence or because of a lack of information is possible: consider as high risk.[17]				

13 Appropriate production processes may vary according to the BSE status of the source region or country and the type of material used (bones and/or hides).

14 Specified risk materials refer to the tissues listed in the opinion adopted on 8-9.12.97 and amended on 19-20.02.98. 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.

15 For placing pharmaceutical products on the market.

16 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. *As an application of the latter principle, and according to the SSC opinion of 22-23.10.98 on The Safety of Bones Produced as a By-product of the DBES, bones (except skull and vertebral column) from animals that comply with the conditions set out in the UK DBES, can be used. The criteria for use should comply with the criteria set out in the above section 7.8.2 for lower risk countries and in the annex to the opinion of 22-23.19.98.*

17 This statement does not prejudge the opinion of the SSC on the TSE/BSE status of any country.

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