

The Removal and Inactivation of Potential TSE Infectivity by the Different Gelatin Manufacturing Processes

A Summary of the Results of different Parts of the comprehensive GME Study

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Introduction

This document summarizes the results of a comprehensive study designed to assess the extent to which the gelatin manufacturing process is capable of inactivating potential BSE infectivity.

Gelatin is a natural, soluble protein, gelling or non-gelling, obtained by partial hydrolysis of the collagen contained in bones or skins of mainly bovine and porcine origin. The safety of gelatin from the perspective of BSE risk depends on a few basic points:

- The health of the animals from which the raw materials originate.
 - The European gelatin manufacturing process uses only raw materials from healthy animals that have been released for human consumption based on rapid BSE-testing.
- The country of origin of the animals.
 - The gelatin manufacturing process does not use raw materials from countries categorized at the highest level of the European Union's Geographical BSE Risk (GBR) system.
- The type of the raw material used.
 - The gelatin manufacturing process does not use raw materials that present a significant risk of transmitting any potential BSE infectivity.
- The manufacturing process and its ability to remove and/or inactivate infectivity.
 - As confirmed by validated studies described in this document, the gelatin manufacturing process removes and inactivates any significant potential infectivity.
- The route of administration (i.e., injection, oral, topical).
 - Most gelatin products are intended for oral use.
- A potential species barrier (i.e., a reduced risk of infection in humans by a bovine-origin disease).
 - Most gelatin products are intended for human use.
- Quantity and frequency of use.

There are, then, a number of factors that contribute to the BSE safety of gelatin. Most importantly, because of the extensive controls on bovine products for food use that are in place in the EU, it is exceedingly unlikely that any BSE infectivity could be present in the raw materials used to produce bovine-origin gelatin. The studies described in this summary were conducted in order to determine the extent to which, if any infectivity were present in the raw materials, the gelatin manufacturing process could eliminate it. As we will describe, these studies show that the gelatin manufacturing process removes and inactivates any significant potential infectivity.

Background

Since 1994 the gelatin industry has implemented various activities to increase the safety of its raw materials. It has also investigated the extent to which any potential TSE infectivity, which could theoretically be associated with bovine bone raw materials, would be removed and/or inactivated by different steps of the gelatin manufacturing process. The industry's research has included (1) evaluation of published results of the effects on infectivity of procedures similar to those used during the gelatin manufacturing process, (2) a study of the removal of central nervous system (CNS) tissue during the degreasing process used for bovine bones, and (3) studies of scrapie strain-infected brain of test animals treated according to the gelatin extraction and liming conditions, to assess the extent to which the treatments reduce the infectivity level.

This body of knowledge has led to the conclusion by a number of health authorities throughout the world that bovine bone gelatins made from appropriate raw materials and manufactured according to certain standard procedures are safe and are very likely to present no concerns regarding the transmission of BSE to humans.

In order to further improve the comparability of test designs to the actual bone gelatin manufacturing process, the industry decided to undertake new confirmatory studies using laboratory scale gelatin manufacturing equipment and procedures which closely reflect actual production scale processes.

GME therefore commissioned with the financial support of the European Commission's "Life Sciences Research Program" a comprehensive study to evaluate the BSE removal and/or inactivation ability of all applied gelatin production processes. Based on a study protocol, reviewed by international experts, these studies have been carried out in three different internationally well recognized and specialized laboratories:

- Institute of Animal Health, Edinburgh, United Kingdom
- ID-Lelystad, Lelystad, Netherlands
- Baltimore Research and Education Foundation, Inc., Baltimore, Maryland, United States of America

Virtually all of these studies have now been completed, using both Scrapie and BSE infectivity, in parallel, for spiking of the bovine bones to compare and control the effect of the gelatin production process on different TSE strains.

In order to show the capacity of the gelatin manufacturing process to remove and/or inactivate infectivity and to demonstrate the safety of the product, the following research conditions were chosen:

- a) The studies were carried out using the highest applicable starting TSE titer, as if all animals used were clinically infected with BSE and no spinal cord or dorsal root ganglia were removed.
- b) Spiking was performed on the same raw material as used in gelatin production.
- c) Testing conditions were validated against the manufacturing conditions in individual commercial gelatin plants by an independent and specialized quality validation institute.
- d) Infectivity testing of the gelatin was done by intracerebral injection of rodents.
- e) Incubation was carried out within the same species, which means that there was no species barrier effect.
- f) The incubation period was at least 600 days, which is more than the longest observed and published period after which an infection was developed in the relevant rodent species by these agents.

Importantly, these conditions reflect a hypothetical “worst case scenario” which has never and could never occur under realistic conditions. In particular, because of the extensive controls on bovine products for food use that are in place in the European Union, it is unlikely that BSE infectivity could be present in the raw materials used to produce bovine-origin gelatin.

The results of five separate studies are summarized below, followed by an overall discussion based on all of the studies. In summary, the studies show that, using current gelatin manufacturing processes, finished gelatin contains no detectable BSE infectivity. These studies demonstrate that gelatin is safe and presents no meaningful risk of transmitting any theoretical BSE infectivity that might be present in raw materials under realistic conditions.

1. Complete Limed Bone Gelatin Process (Tested with mice 301V BSE strain)

Summary Report

The industrial manufacturing process for the production of limed bone gelatin was downscaled to an accurate laboratory scale model. Using this laboratory model process, the experimental gelatin was manufactured from a mixture of vertebral bones containing spinal cord that had been artificially contaminated with mouse-brain, infected with the 301V strain of mouse-passaged BSE agent, and industrial crushed but not degreased bones contaminated on the surface with the infective agent. The total quantity of infective material was with 0,5% by weight about equivalent to the quantity of spinal cord and dorsal root ganglia that were included in

the industrial bones before the removal was implemented in 1998. Of course, unlike the infective material used in the study, the spinal cord and dorsal root ganglia in industrial bones at that time were unlikely to be infective. A variety of different sample materials were taken throughout the experimental process and the conditions were constantly compared to those of the actual gelatin production process. To determine the capacity of the process to remove/inactivate 301V infectivity, the following were bio-assayed to determine the amount of infectivity present: (1) samples of the infectious brain used for spiking, (2) the unpurified gelatin extract, and (3) the concentrated, purified (filtered and deionized) and sterilized gelatin. The infectivity present in these samples was determined by intracerebral inoculation in experimental mice. The infectivity measured in the infectious brain was $10^{7.7}$ ID₅₀/g. In the extracted gelatin before purification infectivity was significantly reduced though still detectable, at $10^{1.8}$ ID₅₀/g. No infectivity was detected in the final purified and sterilized gelatin ($\leq 10^{1.3}$ ID₅₀/g).

The calculated clearance factors were: $10^{3.7}$ ID₅₀ for the process steps (degreasing, acid treatment and liming) up to extraction and $\geq 10^{4.9}$ ID₅₀ for the complete process following purification, concentration and sterilization.

In this study, the finished gelatin product, intracerebrally injected, did not cause any clinical BSE signs in the test animals, nor was any infection detectable histopathologically in the mouse brains, after more than 600 days following inoculation.

Conclusions

1. The laboratory model of the limed bone gelatin manufacturing process removed/inactivated an extremely high 301V BSE infective dose to below the level of detection after intracerebral injection into the same animal species.
2. The measured 301V infectivity reduction of more than $10^{4.9}$ ID₅₀ was the maximum that could be measured between the extremely high spiking level and the detection limit. The capacity of infectivity reduction by the total process may be higher, but this cannot be measured using this type of study design, which is the best and most sensitive currently available.
3. 301V BSE infectivity was decreased substantially, by a factor of $10^{3.7}$, by the first steps of the process: degreasing, demineralization, liming and final washing. Most of the applied infectivity was already removed/inactivated by these process steps.
4. BSE infectivity is somewhat more resistant to the chemical treatment during the gelatin process as compared with the results of our tests with Scrapie infectivity.
5. Purification of the gelatin extract (filtration, ion-exchange and UHT-sterilization) contributes further to the removal/inactivation of infectivity. In this type of study the infectivity reduction of this part of the process can only be measured as a difference between the infectivity remaining in the gelatin extract and the detection level. In fact, the actual effect is at least about 1 log₁₀ greater infectivity reduction than could be measured in this part of the study, as can be seen from the results of the acid bone gelatin process study (discussed below).

6. The gelatin manufacturing process was successfully scaled down; gelatin was prepared from industrial starting material.
7. The study complies with the requirements of a validation study.
8. The study design has simulated in its starting infectivity level a situation which was at least 10,000 times worse than the industrial situation at any time in continental Europe. Despite this unrealistically high infective level, the final gelatin was not able to induce a TSE disease in any test animal. Neither clinical signs nor typical pathological signs have been found in the mouse brains.

In conclusion, these data provide actual measurements of clearance factors for the alkaline bone gelatin manufacturing process that can be used to facilitate a risk assessment of the safety of bovine derived bone gelatin with regard to BSE and human safety under realistic conditions.

2. Limed Bone Gelatin Process until Extraction (Tested with hamster 263K Scrapie strain)

Summary Report

The industrial manufacturing process for the production of limed bone gelatin was downscaled to an accurate laboratory scale model. Using this laboratory model process, experimental gelatin was manufactured from a mixture of vertebral bones containing spinal cord that had been artificially contaminated with hamster-brain infected with the 263K strain of hamster-passaged Scrapie agent, and industrial crushed but not degreased bones contaminated on the surface with the infective agent. The total quantity of infective material was with 0,5% by weight about equivalent to the quantity of spinal cord and dorsal root ganglia that were included in the industrial bones before the removal was implemented in 1998. Of course, unlike the infective material used in the study, the spinal cord and dorsal root ganglia in industrial bones at that time were unlikely to be infective. Different sample materials were taken and throughout the experimental process the conditions were constantly compared to those of the actual gelatin production process. To determine the capacity of the process to remove/inactivate 263K Scrapie infectivity, samples of the infectious brain used for spiking and of the unpurified gelatin extract were bio-assayed for the amount of infectivity present. The infectivity present in these samples was determined by intracerebral inoculation in experimental hamsters. The infectivity measured in the infectious brain was $10^{8.0}$ ID₅₀/g. This level was significantly reduced in the extracted gelatin before purification, measured at $10^{1.1}$ ID₅₀/g. The calculated clearance factor was $10^{4.6}$ ID₅₀ for the process steps (degreasing, acid treatment and liming up to the point of extraction) after more than 600 days following inoculation.

Conclusions

1. The laboratory model of the limed bone gelatin manufacturing process (processed until the point of extraction of the gelatin, without purification) removed and/or inactivated an extremely high 263K Scrapie infective dose to a point close to the

limit of detection after intracerebral injection into the same animal species.

2. The measured 263K Scrapie infectivity reduction of $10^{4.6}$ ID₅₀ was obtained by the scaled down model of the limed bone gelatin manufacturing process until extraction.
3. 263K Scrapie infectivity was decreased substantially by the first steps of the process: degreasing, demineralization, liming and final washing. Most of the applied infectivity was already removed/inactivated by these process steps. The factor $10^{4.6}$ is in line with the results of other studies commissioned by GME several years ago (see introduction).
4. 263K Scrapie infectivity is apparently somewhat less resistant to the chemical treatment during the gelatin process as compared with 301V BSE infectivity.
5. The effect of purification of the gelatin extract (i.e., filtration, ion-exchange and UHT-sterilization) was not tested in this part of the study. Based on the results of the other experiments done, one could reasonably expect that after purification and sterilization this gelatin would also not have induced disease in the test animals after inoculation.
6. The gelatin manufacturing process was successfully scaled down; crude gelatin was prepared from industrial starting material.
7. The study complies with the requirements of a validation study.
8. The study design has simulated in its starting infectivity level a situation which was at least 10,000 times worse than the industrial situation at any time in continental Europe. Despite this unrealistically high infective level, the infectivity of the unpurified and unsterilized gelatin was substantially reduced, close to the detection limit.

In conclusion, these data provide actual measurements of clearance factors for the alkaline bone gelatin manufacturing process that can be used to facilitate a risk assessment of the safety of bovine derived bone gelatin with regard to BSE and human safety under realistic conditions.

3. Complete Acid Bone Gelatin Process (Tested with mice 301V BSE strain)

Summary Report

The industrial manufacturing process for the production of acid bone gelatin was downscaled to an accurate laboratory scale model. Using this laboratory model process, experimental gelatin was manufactured from a mixture of vertebral bones containing spinal cord that had been artificially contaminated with mouse-brain infected with the 301V strain of mouse-passaged BSE agent, and industrial crushed but not degreased bones contaminated on the surface with the infective agent. The

total quantity of infective material was with 0,5% by weight about equivalent to the quantity of spinal cord and dorsal root ganglia that were included in the industrial bones before the removal was implemented in 1998. Of course, unlike the infective material used in the study, the spinal cord and dorsal root ganglia in industrial bones at that time were unlikely to be infective. A variety of different sample materials were taken throughout the experimental process and the conditions were constantly compared to those of the actual production process. To determine the capacity of the process to remove/inactivate 301V BSE infectivity, samples of the infectious brain used for spiking, the unpurified gelatin extract, and the concentrated and purified (filtered, deionized and sterilized) gelatin were bio-assayed for the amount of infectivity present. The infectivity present in these samples was determined by intracerebral inoculation in experimental mice. The infectivity measured in the infectious brain was $10^{7.8}$ ID₅₀/g, in the extracted gelatin before purification it was $10^{2.8}$ ID₅₀/g, while no infectivity was detected in the final purified and sterilized gelatin ($\leq 10^{1.3}$ ID₅₀/g).

The calculated clearance factors were: $10^{2.6}$ ID₅₀ for the process steps (degreasing and acid treatment) up to extraction and $\geq 10^{4.8}$ ID₅₀ for the complete process following purification, concentration and sterilization. In this study, the finished gelatin product, intracerebrally injected, did not cause any clinical BSE signs in the test animals, nor was an infection detectable histopathologically in the mouse brains, after more than 600 days following inoculation.

Conclusions

1. The laboratory model of the acid bone gelatin manufacturing process removed/inactivated an extremely high 301V BSE infective dose to below the limit of detection after intracerebral injection into the same animal species.
2. The measured 301V BSE infectivity reduction of more than $10^{4.8}$ ID₅₀ was the maximum that could be measured between the extremely high spiking level and the detection limit. The capacity of infectivity reduction of the total process may be higher, but this cannot be measured by this type of study design, which is the best and most sensitive currently available.
3. 301V BSE infectivity was reduced by a factor of $10^{2.6}$ by the first steps of the process (degreasing and acid treatment until extraction). A significant portion of the applied infectivity was already removed/inactivated by these process steps. This is in line with the results of other studies commissioned by GME some years ago.
4. Purification of the gelatin extract (i.e., filtration, ion-exchange and UHT-sterilization) contributes further to the removal/inactivation of infectivity. In this type of study, the infectivity reduction of this part of the process can only be measured as the difference between the infectivity remaining in the gelatin extract and the detection level. In this case the remaining infectivity (after extraction of the gelatin) of 2.8 log 10/g was completely inactivated, compared with only 1.8 log 10 remaining in the limed bone gelatin experiment after extraction. The real effect might be even higher, but it is not measurable in this study design.
5. This makes it very likely that the inactivation/removal potential of the limed bone process is higher than the $10^{4.9}$ which could be measured as a maximum in that

part of the study.

6. The gelatin manufacturing process was successfully scaled down; gelatin was prepared from industrial starting material.
7. The study complies with the requirements of a validation study.
8. The study design has simulated in its starting infectivity level a situation which was at least 10,000 times worse than the industrial situation at any time in continental Europe. Despite this unrealistically high risk level, the final acid bone gelatin was not able to induce a BSE disease in any test animal. Neither clinical signs nor typical positive reactions have been found by pathological brain testing.

In conclusion, these data provide actual measurements of clearance factors for the acid bone gelatin manufacturing process that can be used to facilitate a risk assessment of the safety of bovine derived bone gelatin with regard to BSE and human safety under realistic conditions.

4. Acid Bone Gelatin Process with NaOH Pre-treatment until Purification (Tested with mice 301V BSE strain)

Summary Report

The industrial manufacturing process for the production of acid bone gelatin including a short time NaOH pre-treatment of the ossein was downscaled to an accurate laboratory scale model. Using this laboratory model process, experimental gelatin was manufactured from a mixture of vertebral bones containing spinal cord that had been artificially contaminated with mouse-brain infected with the 301V strain of mouse-passaged BSE agent, and industrial crushed but not degreased bones contaminated on the surface with the infective agent. The total quantity of infective material was with 0,5% by weight about equivalent to the quantity of spinal cord and dorsal root ganglia that were included in the industrial bones before the removal was implemented in 1998. Of course, unlike the infective material used in the study, the spinal cord and dorsal root ganglia in industrial bones at that time were unlikely to be infective. Different sample materials were taken throughout the experimental process and the conditions were constantly compared to those of the actual gelatin production process. To determine the capacity of the process to remove/inactivate 301V BSE infectivity, samples of the infectious brain used for spiking and the unpurified gelatin extract were bio-assayed for the amount of infectivity present. The infectivity present in these samples was determined by intracerebral inoculation in experimental mice. The infectivity measured in the infectious brain was $10^{7.7}$ ID₅₀/g, in the extracted gelatin before purification no infectivity was detected ($\leq 10^{0.3}$ ID₅₀/g). The calculated clearance factor for this process until extraction was $\geq 10^{5.4}$ ID₅₀. In this study, the finished gelatin product, intracerebrally injected, did not cause any clinical BSE signs in the test animals, nor was an infection detectable

histopathologically in the mouse brains, after more than 600 days following inoculation.

Conclusions

1. The laboratory model of the acid bone gelatin manufacturing process including a short time NaOH treatment of the demineralized bones until extraction, but without further purification, removed/ inactivated an extremely high 301V BSE infective dose to below the limit of detection after intracerebral injection into the same animal species.
2. The measured 301V infectivity reduction of more than $10^{5.4}$ ID₅₀ was the maximum that could be measured between the extremely high spiking level and the detection limit. The capacity of infectivity reduction of the total process including the purification and sterilization steps may be higher, but this cannot be measured by this type of study design, which is the best and most sensitive currently available.
3. 301V BSE infectivity was decreased by a factor of $10^{5.4}$ by the first steps of the process (degreasing, demineralization and NaOH pre-treatment until extraction). The additional clearance factor achieved for the short application of NaOH treatment was 2.8 log 10. This is in line with other published inactivation studies and the results of studies commissioned by GME and Leiner Davis Gelatin Ltd. some years ago.
4. Purification of the gelatin extract (i.e., filtration, ion-exchange and UHT-sterilization) would have contributed further to the removal/inactivation of infectivity of this type of gelatin, but would not have been measurable in this study. In this type of study, the infectivity reduction of this part of the process can only be measured as the difference between the infectivity remaining in the gelatin extract before purification and the detection limit in the purified final gelatin. In this case, no infectivity remained after extraction and before purification.
5. The gelatin manufacturing process was successfully scaled down; gelatin was prepared from industrial starting material.
6. The study complies with the requirements of a validation study.
7. The study design has simulated in its starting infectivity level a situation which was at least 10,000 times worse than the industrial situation at any time in continental Europe. Despite this unrealistically high risk level, the final acid bone gelatin was not able to induce BSE disease in any test animal. Neither clinical signs nor typical positive reactions have been found by pathological brain testing.

In conclusion, these data provide actual measurements of clearance factors for the acid bone gelatin manufacturing process with a short time NaOH pre-treatment included, that can be used to facilitate a risk assessment of the safety of bovine derived bone gelatin with regard to BSE and human safety under realistic conditions.

5. Heat and Pressure Bone Gelatin Process until Extraction (Tested with mice 301V BSE strain)

Summary Report

This newly developed, industrial production process for the manufacturing of gelatin with low gelling power, applied by one GME member, was scaled down to an accurate laboratory scale model. Using this laboratory model process, experimental gelatin was manufactured from a mixture of vertebral bones containing spinal cord that had been artificially contaminated with mouse-brain infected with the 301V strain of mouse-passaged BSE agent, and industrial crushed but not degreased bones contaminated on the surface with the infective agent. The total quantity of infective material was with 0,5% by weight about equivalent to the quantity of spinal cord and dorsal root ganglia that were included in the industrial bones before the removal was implemented in 1998. Of course, unlike the infective material used in the study, the spinal cord and dorsal root ganglia in industrial bones at that time were unlikely to be infective. Different sample materials were taken and throughout the experimental process conditions were constantly compared to those of the actual gelatin production process. To determine the capacity of the process to remove/inactivate 301V BSE infectivity, samples of the infectious brain used for spiking and the unpurified gelatin extract were bio-assayed for the amount of infectivity present in each. The infectivity present in these samples was determined by intracerebral inoculation in experimental mice. The infectivity measured in the infectious brain was $10^{8.7}$ ID₅₀/g, while no infectivity was detected in the extracted gelatin before purification ($\leq 10^{0.2}$ ID₅₀/g). In this study, the finished gelatin product, intracerebrally injected, did not cause any clinical BSE signs in the test animals, nor was an infection detectable histopathologically in the mouse brains, after more than 600 days following inoculation.

The detection limit in this part of the study was less than or equal to $10^{0.3}$. This was similar to that for other studies and reflects that the extract could be injected without further dilution.

The calculated clearance factor was greater than or equal to $10^{6.8}$ ID₅₀ for the process steps (i.e., degreasing, heat and pressure treatment) up to extraction, before purification.

Conclusions

1. The laboratory model of the heat-and-pressure bone gelatin manufacturing process, before purification, removed/inactivated an extremely high 301V BSE infective dose to below the limit of detection after intracerebral injection into the same animal species.
2. The measured 301V BSE infectivity reduction of more than $10^{6.8}$ ID₅₀ was the maximum that could be measured between the extremely high spiking level and the detection limit. The capacity of infectivity reduction of the total process including purification may be higher, but this cannot be measured by this type of study design, which is the best and most sensitive currently available.

3. 301V BSE infectivity was significantly decreased, by a factor of $10^{6.8}$ by the first steps of the process (degreasing and heat and pressure treatment). All of the applied infectivity was already removed/inactivated by these process steps below the detection limit.
4. Purification of the gelatin extract (i.e., filtration and ion-exchange) were not applied and tested in this part of the study because no further reduction of infectivity would have been measurable.
5. The gelatin manufacturing process was successfully scaled down; gelatin was prepared from industrial starting material.
6. The study complies with the requirements of a validation study.
7. The study design has simulated in its starting infectivity level a situation which was at least 10,000 times worse than the industrial situation at any time in continental Europe. Despite this unrealistically high infective level, the unpurified gelatin was not able to induce a BSE disease in any test animal. Neither clinical signs nor typical positive reactions have been found by pathological brain testing.

In conclusion, these data provide actual measurements of clearance factors for the special bone gelatin manufactured by the heat and pressure process that can be used to facilitate a risk assessment of the safety of this specific bovine derived bone gelatin with regard to BSE and human safety under realistic conditions.

Summary of Conclusions and Compliance with other studies

1. All gelatin manufacturing processes tested, using artificially high infective raw material, have resulted in a final gelatin which, after purification, has not induced a TBSE disease after intracerebral injection in animals of the same species.
2. Pathological brain investigation has also not indicated pre-clinical infection of the test animals.
3. The applied starting level of infectivity of the experimental raw material was as high as if all actual bovine animals used for production were clinically infected and infective spinal cord and dorsal root ganglia were not removed.
4. The infectivity applied by the test raw material was at least 10,000 times higher than could theoretically have been possible at any time in continental Europe. Under realistic conditions, because of the extensive controls on bovine products for food use that are in place in the EU, it is unlikely that BSE infectivity could be present in the raw materials used to produce bovine-origin gelatin.
5. 301 V BSE infectivity is, based on our results, somewhat more resistant against chemical treatments than 263K Scrapie infectivity
6. The results of the above-described studies are similar to those achieved in previous studies which evaluated (1) the removal of CNS during degreasing (1.5

log₁₀), and (2) infectivity reduction under acidulation conditions (1 log₁₀) and liming conditions (2 log₁₀) of bones using Scrapie infected brain. If those results were additive, the cumulative infectivity reduction resulting from these processing steps would have been 4.5 log₁₀. The clearance factor of the same production steps in the new study with the 263K Scrapie strain is 4.6 log₁₀.

7. The better effect in BSE infectivity reduction by the NaOH treatment compared with lime was expected due to the higher pH of the caustic soda and also based on previous study results of the gelatin industry in which lime and caustic were applied to experimentally Scrapie infected mouse brain.
8. The results have proven that gelatin manufacturing from highly (and unrealistically) infective raw material, under manufacturing processes that represent the minimum conditions used by the European industry, has resulted in finished products that do not induce a TSE disease. This indicates that under normal raw material sourcing conditions, in which it is unlikely that BSE infectivity would be present, the safety margin of bone gelatin for all applications is extremely high.
9. This was confirmed by the Scientific Steering Committee of the European Union as well which, when stating their opinion on the safety of gelatin, commented: "The risk is close to zero"