



The use of collagen from hides of UK cattle

Issue

1. The Bovines and Bovine Products (Trade) Regulations 1999 (BBPT Regulations) prevent the supply of **collagen** derived from hides of **UK bovines** to the **UK market for non-technical uses**. Non-technical uses include food, animal feed, cosmetics, and medical and pharmaceutical products.
2. The Department for Environment, Food and Rural Affairs (Defra) have received a request from a UK based company that would like to commence sourcing collagen from the hides of UK bovines for non-technical uses for the domestic market place. Such a request would require an amendment to the current BBPT Regulations. Defra has asked for SEAC advice on whether amending the regulations to allow collagen for non-technical uses derived from hides of UK bovines would increase the level of risk to UK consumers. SEAC have not previously considered the level of risk relating to collagen sourced from UK bovines.

Background

Collagen

3. Collagen¹ is a family of fibrous proteins, with a high tensile strength which are found in connective tissues such as the organic matrices of hides, bones, tendons, cartilage, cornea of the eye, blood vessels and teeth.
4. Collagen is used for a number of purposes, e.g. sausage casings, cosmetics, and in vascular surgery as collagen coated grafts, collagen aortic heart valves, corneal shields, other prosthetics, catgut, catheter cuffs, collagen based wound dressings, collagen products for hard tissue repair, periodontal ligament repair, bulking

¹ Definition of collagen from the "Updated Report and Scientific Opinion on the safety of hydrolysed proteins produced from bovine hides. Adopted by the Scientific Steering Committee at its meeting of 22-23 October 1998 and updated at its meeting of 25-26 May 2000.

agents for incontinence. Collagen is also used as a soluble injectable carrier of antibiotics and used in drug delivery.

Production process of collagen

5. Collagen is mainly derived from skins and hides of ruminants. For bovine collagen production, the animals are skinned after slaughter, but before the carcasses are opened. The hides, before being further processed, are washed and typically cooled or treated with alkali.
6. According to the EU Scientific Steering Committee (SSC) opinion on the safety with respect to TSE risks of collagen from ruminant hides (10 – 11 May 2001), the production of collagen generally involves an alkali processing at pH 11.5-13 for 24-48 hours and pH 13.0 for 12-13 hours (with lime or a lime of sodium sulphide solution or diluted sodium hydroxide). The extraction of collagen from bovine skins is carried out with HCl for gel formation at pH between 0.8-3.3 during 6-48 hours at room temperature.

EU regulatory controls

7. In March 1996 a EU Commission Decision 96/239 (later revised as Decision 98/256) instituted a ban on the exports of beef and beef products from the UK to other Member States and third countries. This legislation also includes a ban on the export from the UK of UK bovine collagen for non-technical uses (human food, animal feed, cosmetics, and medical and pharmaceutical products). It does not however prohibit such uses of UK collagen on the domestic market.²

UK regulatory controls

8. In 1999 the UK legislation, BBPT Regulations, went further than the EU requirements by prohibiting the production of collagen from UK bovine hides for non-technical uses. This was a **risk management** measure to assist enforcement and compliance with the EU ban on UK exports of non technical use products derived from UK sourced collagen. The implementation of this legislation was not based on a scientific risk assessment. This measure currently remains in force and will require amendment, if UK sourced collagen for non-technical uses is to be permitted in the domestic market.

² Confirmation from Commission legal services that this is indeed the case is currently awaited.

9. For information, the later EU TSE Regulations, No. 999/2001, of 22 May 2001 places no restriction on trade in such collagen. This regulation, was based at least in part on opinion of the Scientific Steering Committee. However, the UK beef ban (Decision 98/256), is still in force and this takes legal precedence over the TSE Regulation. The EU Commission subsequently proposed an amendment to Decision 98/256 to bring it into line with the SSC opinion and TSE Regulation by permitting the UK to export collagen. However, EU legal advisers blocked this proposal on technical legal grounds. As such, the ban on the export from the UK of UK bovine collagen for non-technical uses (human food, animal feed, cosmetics and medical and pharmaceutical products) still remains in place.
10. The EU Commission recently implemented new EU wide control measures for collagen production, by amending Council Directive 92/118/EEC regarding the requirements for collagen intended for human consumption (Commission Decision 2003/721/EC). The additional control measures include:
- All hides are veterinary certificated as coming from animals "which have been slaughtered in a slaughterhouse and whose carcasses have been found fit for human consumption following ante and post mortem inspection".
 - All tanneries are now subject to audit and must register to supply collagen for human consumption.
 - All manufacturing facilities are subject to audit and require an authorization number in addition to registration with the FSA.
 - All finished products must now meet stringent analytical and microbiological criteria.

Request to use collagen derived from UK bovines

11. Until recently, a UK based company involved in collagen production sourced sufficient supplies of collagen, for non-technical use products, from designated BSE free countries to satisfy their markets. Following confirmation of the first case of BSE in the United States, the supply chain for collagen from this designated low risk of BSE country has decreased.

12. The UK company also source collagen from EU countries where the incidence of BSE in post 1996 animals is comparable to that of the UK. The UK company would like to commence using collagen derived from hides of UK bovines for the UK market for non-technical uses. This would increase their overall supply and provides more flexibility to meet the demands of their customers.

Current scientific opinion

13. There are three main factors that need to be considered in terms of assessing the risk from collagen in relation to BSE:

- The presence of the BSE agent and titre of infectivity likely to be found in the skins and hides used in collagen production.
- The effectiveness of the process used for the inactivation (or the elimination) of the agent.
- The application or end use (i.e., food, feed, cosmetics, medicinal products and devices, technical uses).

It is worth noting that the sourcing of collagen will be derived from animals designated for human consumption.

Opinion of the EU Scientific Steering Committee

14. On 10 – 11 May 2001, the EU Scientific Steering Committee adopted a scientific report and opinion on 'The Safety with respect to TSE Risks of Collagen produced from Ruminant Hides'. The SSC opinion was adopted on the basis of the report prepared by the TSE/BSE *ad hoc* Group. The main points of the SSC opinion are reproduced below:

- ***Risk relating to the raw material*** - *On the basis of current knowledge it can be considered that the parts of ruminant hides used for the production of collagen do not present a risk with regard to TSEs, provided contamination with potentially infected materials is avoided. The risk of contamination of skin with TSE agent by spillage of blood and/or CNS tissues is small if slaughter and skinning are appropriately performed.*

- **Production process** - Some production processes reduce TSE infectivity and could therefore provide additional safety if the risk of contamination of the raw material is not excluded. Several collagen manufacturing processes exist, but according to available information no TSE inactivation experiments have been carried out with ruminant hides.
- **Collagen for human consumption and cosmetics** – For countries where the presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a region or country is highly unlikely (Geographical BSE Risk (GBR) 1) hides could in principle be sourced from any animal. Sourcing from animals that passed the ante-mortem inspection as fit for human consumption would add additional safety. For other countries, hides should be sourced only from animals that passed the ante-mortem inspection as fit for human consumption. The risk of cross contamination with specified risk materials or potentially contaminated materials should be minimal. This implies that slaughter methods should be such that the risk of contamination should be minimal. The exclusion of “healthy” animals but that tested positive for a recognised BSE post-mortem test, will further reduce the risk.
- **Collagen in registered pharmaceutical products and for parenteral use** – Collagen in pharmaceuticals may be administered by oral, topical or parenteral route and the requirements for its quality are governed by Commission Directive EC 75/318. 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 collagen for use in pharmaceuticals may therefore vary according to the route or site of application.

The SSC considers that the conditions as specified for food and cosmetics should apply for collagen for oral or topical use (excluding ophthalmic use). Consideration should be given to the use of a special grade collagen in topical products where these are likely to be applied to large areas of damaged skin or to open wounds.

Collagen for parenteral or ophthalmic administration or for use in implantable devices (including use as excipients in this group of products) are available only through a regulatory case by case process. The SSC considers that a special grade of collagen should be considered for these products containing collagen.

- **Collagen as a reagent in the manufacture of pharmaceuticals**
– Where the end products, for which collagen is needed during the manufacturing process, are for parenteral or ophthalmic use, the Scientific Steering Committee recommends the same stringent conditions should apply as set out for parenteral or ophthalmic administration or for use in implantable devices.
15. The full opinion and report of the SSC on the Safety with Respect to TSE Risks of Collagen produced from Ruminant Hides (10 – 11 May 2001) is at [Annex 1](#).
 16. In considering the risk of ruminant hides for collagen production and the possible reduction of infectivity through processing, the SSC took account of the detailed information contained in other SSC opinions, particularly the opinion on gelatine (EC 2000) and hydrolysed protein (EC 2000). These opinions and reports relate to products sourced and processed in a similar way to collagen. Both reports and opinions are at [Annex 2](#) and [Annex 3](#) respectively and consider in detail the risk of infectivity of bovine hides as the source of the raw material, the production processes involved and the end uses.
 17. The SSC opinion on “The Safety with regard to TSE risks of Gelatine derived from Ruminant Bones and Hides” was last updated and adopted by the SSC at its meeting of 6-7 march 2003. This later opinion states:
 - *The SSC considers that – regardless of type of production process, but assuming that any gelatine from hides production process would have some TSE infectivity reduction capacity at least equivalent to a collagen production process³ – the respect of the recommendations on sourcing listed further on will result in a safe end product.*
 18. A copy of the SSC 2003 opinion on gelatine is attached at [Annex 4](#).

Infectivity levels in bovine tissues

19. Infectivity levels in tissues and parts of an animal are currently based on the mouse and cattle bioassay with intra-cerebral injection of tissue material. Collagen is usually produced from bovine hides and on the basis of current knowledge ruminant hides⁴ are not

³ See SSC opinion of 10 – 11 May 2001 on the Safety with respect to TSE risks of collagen produced from ruminant hides.

⁴ Contrary to findings in cattle with BSE in which the tissue distribution of infectivity is the most limited recorded for any of the TSEs, results of a recent study analysing infectivity in greater kudu (*Tragelaphus strepsiceros*), a non-domesticated bovine from Africa, with BSE showed low titres or traces of BSE infectivity in skin (Cunningham AA. *et al.* paper in press).

considered to be part of the group of tissues that potentially represent a risk with regard to TSEs.

20. On 24th March 1999, the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) adopted an opinion on the Safety of Hides and Skins. SCMPMD was asked whether it was necessary to modify the policy regarding the use of hides and skins for the preparation of gelatine following the publication of a paper by Pammer⁵ *et al* (1999a), which describes the detection of the cellular (non-pathogenic) form of the prion protein (PrP^c) in the skin of humans, mainly keratinocytes, but also in infiltrating mononuclear cells. In respect of the policy regarding the use of hides and skins for the preparation of gelatine, the SCMPMD said:

“Pammer et al. unequivocally demonstrate the presence of PrP^c in the skin. By this finding, they extend the range of tissues known to express PrP^c. The theoretical possibility that skin contains also PrP^{sc}, the pathologic form of the prion protein, or TSE infectivity in significant amounts is not supported by the majority of observations. However, crucial experiments as a search for PrP^{sc} in the skin have not yet been performed. The methods are easily available. Until those studies are completed there is no sound justification for a change in policy regarding the use of hides and skins for the preparation of gelatine.”

21. The executive summary of the SCMPMD opinion and the paper by Pammer *et al* (1999a) are attached at [Annex 5](#) and [6](#) respectively.
22. Pammer *et al* (1999b)⁶ also reported the presence of PrP^c in bovine squamous epithelia in animals without BSE (n=3). Immunohistochemical staining and western blot analysis using an anti-PrP mAb 6H4 showed that PrP^c is present in formalin fixed and cultured keratinocytes respectively.
23. Infectivity was not detected in bioassays carried out on cattle with BSE (Table 1, page 21 - Wells GAH. *et al*, paper in preparation – provided to members and officials in confidence at [Annex 7](#)). The SSC provided an opinion on “TSE infectivity distribution in ruminant tissue” of 10-11 January 2002 and amended at its meeting on 7-8 November 2002. This opinion is attached at [Annex 8](#). For infectivity

⁵ Pammer, J., Weninger, W. and Tschachler, E. :Human keratinocytes express cellular prion-related proteins in vitro and during inflammatory skin disease. American Journal of Pathology 153, 1353-1358, 1998.

⁶Pammer J, Suchy A, Rendl M, Tschachler E. Lancet. 1999 Nov 13;354(9191):1702-3. Cellular prion protein expressed by bovine squamous epithelia of skin and upper gastrointestinal tract.

levels of bovine tissues, this opinion was based on the results of the VLA cattle pathogenesis study at that time.

Advice sought from the committee

24. A UK based company, which processes collagen for non-technical uses, would like to be able to source collagen derived from the hides of UK bovines in order to supplement their current potential countries of intake. The collagen would be sourced from the hides of animals, which are considered fit for human consumption and enter the food supply. Currently, collagen for the domestic market may be sourced from other EU countries where the incidence of BSE post 1996 is comparable to that of the UK.
25. To permit the manufacture of collagen derived from the hides and skins of UK bovine animals for sale in the UK for human food, animal feed⁷, cosmetics or medical or pharmaceutical products would require an amendment to the Bovines and Bovine Products (Trade) Regulations 1999.

The committee is asked to advise on:

Whether a change to the legislation to allow collagen sourced from the hides and skins of UK bovines would increase the level of risk to UK consumers.

If the committee agree a change in the legislation would result in an increase in risk, can they comment on the comparative risk from collagen sourced from other countries.

⁷ This being a specific exception from the EU ban on animal protein in animal feed

List of accompanying material

Annex 1

Opinion and Report on “Safety with Respect to TSE Risks of Collagen produced from Ruminant Hides” adopted by the EU Scientific Steering Committee at its meeting of 10-11 May 2001.

Annex 2

Scientific Report and Opinion on “The Safety of Gelatine” updated by the EU Scientific Steering Committee at its meeting of 20-21 January 2000.

Annex 3

Updated Report and Scientific Opinion on the “Safety of hydrolysed proteins produced from bovine hides”. Adopted by the EU Scientific Steering Committee at its meeting of 22-23 October 1998 and updated at its meeting of 25-26 May 2000.

Annex 4

Updated Opinion on “The Safety with regard to TSE Risks of Gelatine derived from Ruminant Bones or Hides”. Adopted by the Scientific Steering Committee at its meeting of 6 – 7 March 2003.

Annex 5

Executive Summary of the Opinion on the Safety of Hides and Skins adopted by Written Procedure by the Scientific Committee on Medicinal Products and Medical Devices on 24 March 1999 – Executive Summary.

Annex 6

Pammer, J., Weninger, W. and Tschachler, E. :Human keratinocytes express cellular prion-related proteins in vitro and during inflammatory skin disease. American Journal of Pathology 153, 1353-1358, 1998.

Annex 7

Wells, G.A.H., Spiropoulos, J., Hawkins, S.A.C., Ryder, S.J., (2004) Pathogenesis of experimental bovine spongiform encephalopathy (BSE): interim results of infectivity assays in cattle including preclinical infectivity in tonsil and observations on the distribution of lingual tonsil in slaughtered cattle. Paper in preparation.

Annex 8

Update of the Opinion on “TSE Infectivity Distribution in Ruminant Tissues”. Adopted by the EU Scientific Steering Committee at its meeting of 10-11 January 2002 and amended at its meeting of 7-8 November 2002.

Annex 9

Pammer J, Suchy A, Rendl M, Tschachler E. Lancet. 1999 Nov 13;354(9191):1702-3. Cellular prion protein expressed by bovine squamous epithelia of skin and upper gastrointestinal tract.