EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C1 - Follow-up and dissemination of scientific opinions

OPINION AND REPORT ON

SAFETY WITH RESPECT TO TSE RISKS OF COLLAGEN PRODUCED FROM RUMINANT HIDES

ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE

AT ITS MEETING OF 10-11 MAY 2001

OPINION.

In 1998, the Scientific Steering Committee adopted a scientific report and Opinion on The Safety of Gelatine. It does not address the safety of collagen, which is related to gelatine and may derived from similar raw materials. In the present opinion, the Scientific Steering Committee addresses the following questions regarding the safety of collagen produced from ruminant hides:

Can collagen produced from ruminant hides be considered to be free of TSE infectivity? If not, under which condition of sourcing of the material (geographical origin, animal origin, type of tissue) and/or age of the animal and/or production process, can it be considered as safe?

The SSC adopted the opinion hereafter on the basis of the attached report prepared by the TSE/BSE *ad hoc* Group.

A. 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 the skin with TSE agent by spillage of blood and/or CNS tissues is small if slaughter and skinning are appropriately performed.

   However, with regard to hides from small ruminants, t*he SSC's wishes to refer to its Pre-emptive risk assessment* of 8-9 February 2001 *should BSE in small ruminants be found under domestic conditions. It* provides a state of affairs regarding tissue infectivity distribution on the basis of the most recent results of the ongoing experiments on BSE in small ruminants. They seem to indicate that BSE, experimentally transmitted to sheep, is likely to show a disease development comparable to scrapie in sheep and that the BSE agent may therefore be present in peripheral nervous tissues of small ruminants. This would imply that the question on the safety with regard to BSE infectivity of small ruminant hides would need to be re-addressed should it become probable or evident that BSE is present in small ruminants.

B. 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 (*).

   Given the uncertainties / unknown TSE inactivation capacity of the various collagen production processes, only an appropriate combination of safe sourcing and end-use will therefore guarantee a reduction of the residual risk to nearly zero.

   (*) The production of collagen from hides and skins involves always an alkali step - using lime, or a lime sodium sulphide solution or a diluted sodiumhydroxide solution - which can be assumed to have some TSE infectivity inactivation capacity should TSE agent be present by contamination of the hides.

C. The end use of collagen is human consumption as well as cosmetic product

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 (GBR I) 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. (The latter would imply a labelling of the hides so that possibly contaminated hides or batches can be traced back).

D. The end use of collagen is in registered pharmaceutical products and for parenteral use.

Collagen in pharmaceuticals may be administered by the 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 above 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.

E. The end use of the collagen is 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.

Note: If collagen is produced from other sources than ruminant hides, a case by case risk assessment should apply.

REPORT ON SAFETY WITH RESPECT TO TSE RISKS OF COLLAGEN PRODUCED FROM RUMINANT HIDES

I. BACKGROUND AND QUESTION.

In 1998, the Scientific Steering Committee adopted a scientific report and Opinion on The Safety of Gelatine. It does not address the safety of collagen, which is related to gelatine and may derived from similar raw materials.

In the present report, the Scientific Steering Committee addresses the following questions regarding the safety of collagen produced from ruminant hides:

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II. THE PRODUCTION OF COLLAGEN

In order to express an opinion on the safety of collagen it is important to take into account the type of raw material used, the possible TSE infectivity reduction capacities of the existing production processes and the intended end-use of the product.

II.A THE RAW MATERIAL.

The raw material used consists mainly of (as far as known) bovine connective tissue of hides and tendons, calves skins, sheep skins and pig skins. Information on other materials that are possibly used as raw material, was not available to the SSC (e.g. sheep gut, bovine bones).

Ruminant hides are not considered to be part of the group of tissues that potentially represent a risk with regard to TSEs. This has been elaborated on in detail in various SSC opinions, for example, the opinion on gelatine (EC 2000) and hydrolysed protein. (EC 2000)

The SSC opinion of 25-26 May 2000 on *The safety of amino-acids from human hair hydrolysate used in cosmetic product for topical application, with regard to Transmissible Spongioform Encephalopathy risks* states: “The absence of any evidence for the presence of TSE infectivity in hair or skins has been acknowledged by Masters *et al* (1980), the SSC (E.C. 1998, 1999a WHO 1997, OIE 2001, the Scientific Committee for Medicinal Products and Medical Devices (E.C. 1999b) and by EMEA (1992). Similarly, no infectivity was detected in bio-assays carried on the skin of sheep with scrapie (Stamp et al. 1959) and cattle with BSE (SEAC 1994). These skin samples would of course also carry hair, even if they have been shaved. Bovine skin/hair is also reported on in the BSE Progress report of the UK Ministry of Agriculture, Food and Fishery (MAFF 1999) which is

based on the work of the neuropathogenesis unit (NPU) reported in the EC consultation on TSE in 1993 (Fraser and Foster 1994)."

The safety of properly sourced hides and skin is further confirmed in the updated report and scientific opinion of 25-26 May 2000 on *The safety of hydrolysed proteins produced from bovine hides* as well as the opinion of the SSC of 12 January 2001 (E.C., 2001: section on The safety of hydrolysed protein derived from material other than hides and skins).

II.B. THE PRODUCTION PROCESSES.

1. Slaughter and skinning

Animals are skinned after slaughter but before opening the carcass. Also, the hides, before being further processed, are generally salted with NaCl and are always thoroughly washed. However, a lack of appropriate precautions may result in a risk of contamination of hides and skins with potentially infected materials.

2. Further processing

There exist several production processes, which use different techniques. Presently, no fully comprehensive descriptions of the production processes of collagen seem to be available, even not if produced for medical use. For a number of them superficial schematic process descriptions were available. (See also the list of References in Section III)

Data on residual infectivity levels are not available and, according to available information, no TSE inactivation experiments have been carried out for animal-derived collagen.

The production of collagen involves generally 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 done with HCl for gel formation at pH between 0,8- 3,3 during 6-48 h at room temperature.

From evidence available for gelatine, it can be assumed that common collagen production processes will be able to reduce partially TSE infectivity. Ideally, according to recent experiments with gelatine (Grobben *et al*, 2001), a process including a short NaOH (0,3 M; 2 hours; pH13) treatment would result in an infectivity reduction of the infective agent of TSE of more then $10^{5,6}$. However, these process conditions can probably not be generalised because of the variety of existing production systems. Therefore, no general recommendations on "the most appropriate" production process can be made.

II.C. THE INTENDED END-USE.

Aside the use of collagen in sausage casings, a wide use of collagen is known in cosmetics (fascia) and in vascular surgery as collagen coated grafts (bovine-xenografts), collagen aortic heart valves, corneal shields and other prosthesis. Also in other medical

devices as catgut[1], catheter cuffs, collagen based wound dressings (soft tissue repair). Collagen products for hard tissue repair, periodontal ligament repair, dental and neural tissues, bulking agents for incontinence etc. There is also use of soluble injectable collagen as carrier of antibiotics and drug delivery.

It is clear that given this variety of possible uses, which all include a direct oral or parenteral use, the possible residual infectivity should be reduced to the lowest possible level. For medicinal applications, strict sourcing rules should apply in order to reduce the residual risk to nearly zero.

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[1] See also the Opinion of the Scientific Committee for Medicinal Products and medical devices on the Safety of catgut

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