UPDATED SCIENTIFIC REPORT ON THE SAFETY OF MEAT-AND-BONE MEAL DERIVED FROM MAMMALIAN ANIMALS FED TO NON-RUMINANT FOOD PRODUCING FARM ANIMALS

Scientific Steering Committee Meeting of 24-25 September 1998

REPORT FROM THE WORKING GROUP

Preamble:

The safety status with respect to TSE agents is a key-issue in the assessment of the possible risks resulting from the use of rendered mammalian materials such as meat-and-bone meal or organic fertilisers and from the use of fallen stock and various high risk animals or materials for further rendering. In the course of its preparation of scientific reports on the safety of organic fertilisers, meat-and-bone meal for fur animals, with MMBM cross-contaminated animal feedstuffs and fallen stock, the Working Group had therefore to constantly update and verify the validity of its report which served as the basis for the opinion on the safety of mammalian meat-and-bone meal adopted by the Scientific Steering Committee on 26-27 March 1998.

The report hereafter presents an update of this report in the light of the Working Group's discussions between March and September 1998.

1. The question

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

2. Definitions

Fit for human consumption

The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem inspection by a competent veterinary authority and that is certified and identifiable as fit for human consumption on the basis of the existing national and EU legislation. The Working Group stresses that positive identification of material from animals not fit for human consumption should be possible, to avoid such material entering in the food or feed chains. This definition implies that material which was originally derived from animals fit for human consumption, may become unfit for consumption, for example because of inadequate storage or transport conditions. The latter risks should be dealt with in specific opinions or legislation.

Meat and bone meal derived from mammalian animals (MMBM).

The definition and report hereafter do not refer to blood meal.

Meat and bone meal, derived from mammalian animals (MMBM), is defined as processed animal protein intended for animal consumption, or as intermediate product for the production of organic fertiliser or other derived products.

Safely use

In the context of these opinions, only the safety aspects relating to the BSE agent are taken into account. Unless otherwise stated, the microbiological safety of organic fertiliser is not addressed by this opinion.

Specified risk materials or SRMs

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

"133°C/20'/3 bars"

The wording "133°C/20'/3 bars" refers to hyperbaric production process of not less than 133°C during not less than 20 minutes, without air entrapped in the sterilising chamber conditions at not less than 3 bar or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. The lag time needed to reach the core temperature is not included in the time requirement for correct rendering.

Remark: In section 4.3.5 *Elements of the risk assessment: rendering*, the working group further elaborates on the equivalency of the batch and continuous processes, and on the question whether the application of the "133ºC/20'/3 bars" standard as a post-sterilisation phase in stead of applying it during the production process itself, would result in an equivalent inactivation of a TSE agent

3. Background

In the formulation of diets for reared animals, both monogastrics and ruminants, it is rather common practice to include protein sources with high biological value. For this reason, also proteins of animal origin obtained from slaughter residues are used such as:
- meat and bone meals of mammalian origin,
- meals from residues of poultry slaughterhouses,
- blood meals,
- fish meals, etc.

The production of meat meals is closely linked to the meat production process. In cattle, just above 50% of the adult animal body is used for human nutrition in the EU. The rest is processed and employed for different purposes, mainly for animal nutrition, where slaughter residues currently represent a major nutritional source (Table No. 1).

The 2.9 million tons of meat meal produced in the EU originate from slaughter residues. To these one should also add about 1.8 million tons of dead animal carcasses. The use of such an enormous amount of residues for feeding purposes meets two fundamental requirements:

- providing feed of excellent nutritional value;
- ensuring an ecological function.

Table 1: Estimates of the production and use, in 1996, of animal meals in the EU (excluding fish meals) (UNEGA, 1997)

Production	EU (in tons)
Meat and bone meals	2.504.328
Blood meals	107.915
Feather meals	171.036
Poultry meals	124.145
Total production	2.907.424
Total consumption	2.136.464

Epidemiological and direct experimental research showed clearly that the origin and maintenance of the BSE epidemic in the UK was directly linked to the consumption of infected meat and bone meal. A ban on feeding MMBM to ruminants was therefore one of the most essential measures taken in the late eighties by the UK Government to combat the increasing epidemic.

Given the inherent risk linked to feeding of meat-and-bone meal and the appearance of the first BSE cases also in the other EU countries, a ban was made operational in the each of the EU Member States through the transposition of Commission Decision 94/381/EEC.

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

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

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

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

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

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

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

- the laboratory experiments have shown that the thermal treatment at 133°C during 20 minutes on its own cannot guarantee the sterility of the product regarding non conventional transmissible agents (in French: Agents transmissibles non conventionnels, ATNC) *and that its efficacy could vary significantly according to the state of desiccation of the product and its content with lipids (Brown et al., 1990; Wright and Taylor, 1993; Taylor et al., 1995);*

- some of the published work relate to experiments using limited volumes of material; hence the results cannot always be extrapolated with certainty to industrial volumes.

(...) the [Dormont] *Committee recommends the evaluation of procedures susceptible of reinforcing the efficacy of the thermal treatment. (...) On the other hand, the efficacy of a delipidation with solvents followed by a thermal treatment, seems important to be evaluated in comparison with the sole thermal treatment.*[1] *(...) In a more general way, and taking into account the multitude and complexity of the* [existing] *processes, the* [Dormont] *Committee recommends an homologation* [of production processes] *on a case by case basis. The Committee also recommends an homologation of the machinery used in the inactivation processes. (...)*

Similarly, the MDSC/SSC in its opinion on Tallow on 8.09.97 referred to the International Scientific Conference on Meat and Bone Meal (Brussels 1-2 July 1997, E.C., 1997) where the issues related to the inactivation / elimination of the BSE infectious agent where addressed:

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

It can thus be concluded that a production process which respects the conditions of "a maximum particle size 50 mm, a process of 133°C at 3 bars during 20 minutes" is presently the most appropriate one for inactivating / eliminating the BSE infectious agent when producing animal derived products such as MBM, but these conditions as such do not fully guarantee a totally safe product if the raw material was highly contaminated.

The present report therefore addresses the question:

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

4. Identification of possible hazards and elements of risk assessment

[1] Note from the SSC: according to new findings it would appear that the application of hot solvents, followed by heat and steam are not very effective in reducing the infectivity of the rendered material. (Taylor et al., 1997; 1998)

4.1. Introduction

In order to express an opinion on the safety of a product derived from potentially infected material, it is important to consider a number of aspects of the production conditions that may affect the safety of the end product. The risk assessment – and thus the preliminary hazard identification - should take into account the use, the origin and the treatment (infectivity clearance) of the starting material.

Safety of use implies limiting the administration of products of mammalian origin to such a level that the risk for the transmission of infectivity is minimised to the maximum possible level. This level depends upon the final use, the (group of) animal species to which the product is fed and the strain of agent involved (species barrier), the level of infectivity of the starting material (geographical origin; potential level of infectivity of the tissues used as raw material) and upon the infectivity clearance resulting from the processing (rendering). The situation may thus clearly differ depending on the potential degree of infectivity of the starting material (animals, their tissues and their age) in the various countries.

In assessing the risk situation one should further take into account the various risk factors listed in the SSC opinion of 23 January 1998 on BSE risk. These factors are listed hereafter:

1. Structure and dynamics of the cattle, sheep and goat populations
2. Animal trade
3. Animal feed
4. Meat and bone meal (MBM) bans
5. Specified bovine offals (SBO) and specified risk materials (SRM) bans
6. Surveillance of TSE, with particular reference to BSE and scrapie
7. Rendering and feed processing
8. BSE and scrapie related culling

Regarding the BSE related risks for consumers of products derived from bovine material, some of the difficulties or uncertainties that arise are:

- neither the BSE agent nor the conditions under which it expresses itself are known with full certainty; no final dose – infection relations have been established and uncertainty exists regarding the effect of repetitive doses, the interval between these doses, etc.

- although it is proven that infectivity reduction can be achieved during the production process by submitting infected material to certain physical or chemical conditions (e.g., 133°C/20'/3 bars), research results from various laboratories are not always identical. It seems also to be not fully known whether the experimentally observed reduction levels during processing of raw material with an initial given infectivity level, can be simply extrapolated (generalised) for starting material with a higher or lower level of initial infectivity;

- For some (steps in) production processes, infectivity reduction levels have not (yet) been established or published or are still being tested;

- It is not proven that some of the principles of infectivity reduction valid for micro-organisms such as bacteria, are also valid for BSE infected material;

- Concepts on relations between dose and effects which are widely used for assessing human risk associated with chemicals (acute exposure , e.g. LD_{50}, repeated exposure,

e.g. NOEL) and to some extent also for micro-organisms (e.g., ID_{50}) may not necessary be applicable as such to the BSE agent.

- Another aspect which needs verification is whether the mixing of the animal material during MBM production at industrial scale is complete or not. If the mixture is not complete, a non-homogeneous distribution of infectivity may be present in the end product.

- Several experiments on the clearance from TSE infectivity during rendering are reported on in the scientific literature. However the results of these experiments are not necessarily comparable as different materials (tissues, human or animal species) as well as TSE agents or strains (scrapie, BSE, …) were processed. Also, the conditions to which the materials were submitted prior to treatment may have been different (e.g., the chemicals used for their conservation).

- Depending upon the target residual risk level aimed at, the analytical methods presently available to quantify the BSE agent in different materials on a large scale have to be validated and eventually new methods have to be developed. It remains to be verified that the sensitivity (and specificity) of these analytical methods (e.g. detection limit) are compatible with the target residual risk level.

- The exact threshold values for classifying countries or regions into TSE risk categories have not been finalised, nor are the exact infectivity levels of the various specified risk materials exactly known.

Given the above listed uncertainties, the *zero risk approach* would imply that any consumption or use of potentially infected animal material is excluded. In practice, this would mean that no meat could be consumed nor products derived from materials originating from countries or animals with a non-zero BSE risk. The risk level itself would, on the above grounds, be difficult to classify.

The approach of *reducing the risk to the lowest possible* level implicitly accepts that a zero risk is almost impossible to achieve and that zero consumption is unrealistic. But the product should be as safe as possible with current available practices of processing or sourcing.

The quantitative approach starts from the premise that the residual infectivity of a product, by handling and processing of the raw materials, can be reduced to a level which is sufficiently low that it does not constitute a life-time risk for the vast majority of the consumers and that the dose effect relationship of the infectious agent is known. The accepted (theoretical) risk level has to be defined a priori. This level can be expressed as theoretical numbers of people that would be infected by a product with a fixed residual infectivity level per unit weight (unit risk), but also as residual infectivity level per unit weight or volume of a product, complying with the accepted (theoretical) risk level under normal consumption habits. The variation of susceptibility of different individuals may further be taken into account. The approach emphasizes reliance on numerical expression of risk, but does therefore not exclude qualitative expressions of risk nor the provision of indications of attendant uncertainties.

Amongst the advantages / conveniences of the quantitative approach the following can be mentioned:

- The acceptable residual risk level, which is not a scientific issue, can be fixed by policy makers or politicians, for example on ethical and humanitarian grounds, possibly combined with economical and industrial considerations.

- Once all reduction levels (clearance factors) are known, the decision maker can opt for certain combinations of infectivity-reducing measures that eventually should result in the pre-fixed residual infectivity (risk) level. (For example: combinations of safe geographical sourcing and/or removal of SRMs and/or safe production process and/or certified herd origin). This will also avoid that certain costly or irreversible risk-reducing measures are implemented which may eventually appear to be unnecessary.

However, the difficulties that go along with the elaboration of a quantitative assessment are clear from the uncertainties listed above. In addition it should be mentioned that where the prevalence of a disease may be known (e.g., numbers of animals with clinical BSE or humans with clinical CJD), the overall prevalence of infection as such (without necessarily visible symptoms) is not (always) known and this fact makes any quantified risk assessment subject to criticism. It is thus clear that, if one opts for the quantitative approach, a sufficiently large safety margin should be built into the assessment, so as to account for all uncertainties including the unknown exact prevalence of infectivity and the variation in susceptibility of different species and individuals.

So far, the Scientific Steering Committee has opted for the approach of risk reduction to the lowest possible level. The major justification for this approach, which so far has also been applied by the SSC in its opinions on the safety of MBM, tallow, gelatine and dicalcium phosphate, was that as long as the above uncertainties persist and as long as no complete and generally accepted data on reduction levels are available for given production processes, a more quantitative risk assessment (see hereafter) could not yet be realised.

However, in its opinions on the on the Safety of Tallow, Gelatine, Dicalcium phosphate, Meat and Bone Meal, the SSC stated that "*As an alternative, a more detailed quantitative risk analysis should be carried out to assess the remaining risk for a herd or individual animals. 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."

In the sections hereafter, an attempt is made towards a quantified assessment of the safety of meat-and-bone meal following rendering at "133°C/20'/3 bars".

4.2. Hazards

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

- The origin and expansion of the BSE epidemic in the UK was directly linked to the consumption of meat and bone meal;

- The respect of the conditions of "a maximum particle size 50 mm, a process of 133°C at 3 bars during 20 minutes" do not fully guarantee a totally safe product if the raw material was highly contaminated.[2]

- Apart from the major experiment run in Edinburgh (Taylor et al., 1995; MAFF, 1997; Taylor et al., 1997), the number of other scientific experiments looking into the safety of meat and bone meal (and tallow) with regard to TSEs is, to the knowledge of the working group, rather limited. The experiment, because of its scope, size and duration, has not been repeated in other laboratories. Finally, the experimental rendering processes were simulations carried out at pilot scale and the extrapolation of the results (scaling up) into the real operational industrial conditions may not be automatic. No test results, confirming the hypothesis that meat and bone meal produced by a specific process is 100% safe, are available from operational rendering plants and probably never will be. On the other hand, the above pilot-scale experiments were not simply laboratory approximations of rendering processes, but were carried out in actual (although pilot-scale) rendering equipment. In collaboration with the industry it was determined how the pilot-scale equipment could be operated to provide a realistic representation of what occurs in full-scale rendering. Also, most validation studies done on the safety of a wide variety of biopharmaceutical products with respect to TSE agents, are almost always carried out on scaled down versions of the manufacturing processes that are spiked with TSE agents.

- The mouse bioassays that are in most cases carried out to detect TSE infection, may not be (fully) representative for a system of homologous detection between animals of the same species (e.g., from bovine to bovine).The sensitivity of the mouse bioassay for assaying TSE agents from cattle or sheep will be reduced by the species barrier. Cattle-to-cattle transmission of BSE by intracerebral route is known to be about 1.000-fold more effective than cattle-to-mouse transmission by the same route (unpublished data from the UK Central Veterinary Laboratory at Weybridge). Superficially, this might appear to compromise any conclusions drawn from the rendering studies with regard to the safety of meat and bone meal. However, in assessing risks related to the consumption of meat and bone meal, the much greater efficiency of establishing infection in mice by the intracerebral (compared with the oral) route of infection must be considered. For example, the difference in efficiency between these two routes for murine scrapie in mice o is 100.000-fold (Kimberlin, 1996). Also, it has been calculated that the transmission of BSE to mice by the oral route, and across a species barrier, is 200.000-fold less efficient than by intracerebral challenge (Kimberlin, 1994). (This has recently been re-assessed and the efficiency could be much lower than this.) These data seem to indicate that the negative results from the mouse bioassays of meat and bone meal in BSE and scrapie-spiked rendering studies can be viewed with a considerable amount of confidence with

[2] See also the remark to the definition "133°C/20'/3 bars, made in section 3 of the present report.

regard to any risk from infection by its consumption. On the other hand, however, certain strains of natural scrapie are transmitted as easily by the peripheral as by the central route and, for example, the infection of mink by the BSE agent is almost equally effective by the oral route as by the mixed parenteral/intracerebral route (Robinson et al., 1994). The WG-"MBM" notes that the scientific discussion on the absolute and relative differences in infectivity according to the way of transmission (oral or central) and depending upon the species barrier, is not yet conclusive and is still ongoing.

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

- The physico-chemical state of the material (size of the particles, state of desiccation, presence of lipids, ...) may affect the heat transfer.

4.3. Elements of the risk assessment: sourcing

4.3.1. Geographical sourcing

What is important is the incidence of infection, which itself is directly related to the disease incidence and the risk of propagation of infectivity. (See also the SSC opinion on BSE risk of 23 January 1998). The disease incidence figure is thus only a first, but incomplete measure for the probability that a production batch would contain infective material.

Information on the average ("normal practice") number of animals that constitute a batch of raw material is further needed as well as on whether the raw material comes mainly from animals as a whole, or whether offals from a single animal can eventually end up in different batches. (For example: bones from plants deboning whole animals or from butcheries deboning half carcasses.)

4.3.2. Sourcing from certified BSE free individual animals (or herds)

This approach, if properly implemented, should theoretically allow completely safe sourcing. In practice such sourcing may be envisaged in a country or region with comprehensive and detailed data on significant parameters related to the epidemiology of BSE and where safe identification systems attached to a computerised passport with full information on the history of the animal, its movements and origin, are available

4.3.3. Sourcing of materials from potentially BSE infected animals

In its opinion "*Listing of Specified Risk Materials: a scheme for assessing relative risks to man*", adopted on 9 December 1997, he SSC has adopted a table categorising the potential infectivity of different organs in BSE-infected animals. (See table 2) The assessment of the infectivity is based in part on scrapie titres, on the finding of high infectivity in the brain of BSE-affected cattle, on the differential impact of BSE-infective organs on the infection of mice to intracerebral inoculation, on the presumed CJD infectivity of human dura mater based on transplant data and on the effects of the use of

CJD infected human derived pituitary hormone. For practical reasons relating to contamination during the slaughter process, some tissues are categorised at a higher level than warranted by their intrinsic infectivity.

Hitherto there has been a tendency to consider the specified risk materials (SRM) as simply relating to the tissue itself. However, it is now clear that SRMs should not be defined simply on the basis of the grades of infectivity as documented by challenge tests of different tissue extracts. 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.

In a further opinion on BSE risk adopted on 26-27 March 1998 the Scientific Steering Committee considered that by excluding the most infective tissues from the processing chains the risk of transmitting BSE can be considerably reduced. This position is confirmed by recent information which allows quantification of the contribution of the most infective tissues to the overall infective load of an infected bovine (see table 3).

In any case, apart from tissues characterised by high or medium infectivity (belonging to category I and II), the other ones, indeed the majority of them from the point of view of weight, have either an undetectable level of infectivity or the infectifivity is inconsistent and when present has a low titre. The infectivity of the tissues included in category IV is undetectable. It includes those tissues and secretions such as meat and milk which are regarded as safe and can therefore be consumed by man without specified inactivation treatment for TSE agents.

Concerning the mode of administration of the infecting dose or, more precisely, whether the infection develops following the administration of a single infecting dose or whether there is a cumulative effect of "non infecting doses", research carried out on laboratory rodents have not entirely shed light on this problem. The currently available results, based on research carried out by Kimberlin and Walker (1989) have pointed out that the infection is most probably triggered off by a single effective dose.

Table 2: Potential infectivity of different organs in BSE-infected animals

Category	**Organs**
1. High infectivity	a) Bovine brain, eyes, bovine spinal cord and bovine dorsal root ganglia, *dura mater*[1,2], pituitary[1,2], skull[2,3] and bovine vertebral column[2] , lungs[5] b) Ovine/caprine brain, eyes and spinal cord, dorsal root ganglia and vertebral columns[2]; ovine and caprine spleens[4], lungs[5]
2. Medium infectivity	a) Total intestine from duodenum to rectum[6], tonsils b) Bovine spleen, placenta, uterus, fetal tissue[7], adrenal, cerebrospinal fluid, lymph nodes
3. Low infectivity	Liver, pancreas, thymus, bone marrow, other bones[8] nasal mucosa, peripheral nerves
4. No detected infectivity[9]	Skeletal muscle, heart, kidney, colostrum, milk, discrete adipose tissues[10], salivary gland, saliva, thyroid, mammary gland, ovary, testis, seminal testis, cartilaginous tissue, connective tissue, skin, hair, blood clot[11], serum[11], urine, bile, faeces

Where no species specification is given then the tissues refer to bovine, ovine and caprine species.

1. These tissues are included because iatrogenic CJD in humans has been associated with tissues or extracts from humans which were contaminated with CJD agent.
2. These tissues have been moved up 1 to 3 categories because of the possibility of contamination by tissues of higher infectivity during slaughter and their inclusion of dorsal root ganglia. Ovine/caprine spinal cord, dorsal root ganglia and vertebral column are put in this sub-category because they could be infected or contaminated if sheep/goats have in practice become "back infected" with BSE from their feeding on infective bovine products.
3. Definition of Skull: Entire head excluding the tongue.
4. Ovine spleens are included because of the finding of the BSE agent in the spleens of sheep challenged experimentally with large doses of BSE. Caprine have not been tested for infectivity with BSE but showed infectivity for Scrapie. Bovine spleen has been tested and showed no infectivity in the mice test.
5. Lung should be considered in the category if the slaughtering method induces through the stunning/pithing method a transfer of brain through the blood stream into the lung.
6. This applies to cattle only unless sheep and goats are considered to be infected by BSE, in which case there would be a need to remove lymph nodes and thymus also.
7. These may best be considered in the same category as placenta because of the high probability of contamination when removing the placenta at slaughter.
8. The likely presence of bone marrow in long bones now means that these bones, on the basis of potential infectivity in older animals, should be placed in the same category as bone marrow.
9. All materials listed under category 4 have been tested in mice with samples reflecting 0.01-0.1 g of original infective tissue. In such samples infectivity titres 1000 fold lower than in brain cannot be detected by this method. Further improvements in the sensitivity can be expected. This may require the revision of the table of relative infectivity given above.
10. This new term is used to describe those reserves of fat which can be removed readily during slaughter in the abattoir or at meat-cutting plants. It does not refer to lipid extracted from mechanically recovered meat or from many other tissues, or at a later stage in the production process. It presupposed the removal of the key associated lymph nodes.
11. There is some albeit in-conclusive evidence that experimentally circulating peripheral blood mononuclear cells may transmit nvCJD.

Table 3: Relative infectivity of suggested specified risk material from an infected bovine (data provided by SEAC, February 1998; updated, July 1998)

Tissue	Infectivity density ($CoID_{50}/g)_1$	Weight (kg) per Animal of 537 kg	ID_{50} per animal	% of total infective load per animal
Brain	10	0.5	5000	64.0
Spinal cord	10	0.2	2000	2401
Trigeminal ganglia	10	0.02	200	2.4
Dorsal root	10	0.03	300	3.6

ganglia				
Ileum	$3.2*10^{-1}$	0.8	260	3.1
Vertebral column	$3.2*10^{-2}$	5.0	160	109
Spleen	$3.2*10^{-2}$	0.8	26	0.3
Eyes & rest of head	$3.2*10^{-2}$	11.6	370	4.5

[1] *$CoID_{50}$ = Cattle oral Infectious Dose 50%*

4.3.4. Sourcing for age.

In its opinion "Listing of Specified Risk Materials: a scheme for assessing relative risks to man" adopted on 9 December 1997, the Scientific Steering Committee concluded that the intestine of young animals should be seen as a risk, *i.e.* by the oral route from first ingesting BSE-contaminated feed. The central nervous system of cattle is, however, extremely unlikely to be detectably infected below an age of 30 months even in cattle exposed to infection as calves. However, the exceptional animal of 20 months with clinical signs of BSE supports a cautious approach. On this basis, an extremely cautious limit for the CNS as a highly infectious tissue could be set at 12 months and provide considerable reassurance of non-infectivity. In cattle greater reassurance would be derived by limiting the use of the CNS to <6 months. This might only be deemed necessary if animals are derived from high risk geographical areas.

Although the infectious agent by definition transfers from the intestine to the CNS, no BSE infectivity other than CNS-associated ganglia and distal ileum has been documented in cattle during the first 30 months incubation period. This must reflect the very low and/or transient dose of the agent in the intermediate tissues, *e.g.* nerves. Thus age classification of the animal does not allow a differentiation to be made between other tissues with theoretical, but unobserved, infectivity until the CNS, dorsal root ganglia and then eventually the bone marrow become infectious from about 30 months post infection (minimum) onwards (see below).

Experimental BSE in sheep seems to have a similar incubation period to that of scrapie in sheep. So the removal of CNS in sheep and goats over 1 year of age will substantially limit the risk of BSE for humans and animals. In order to improve still further the protection, an even younger age could be chosen, but the additional protection afforded would be very small considering the rarity of scrapie in sheep and goats under 1 year of age and that the studies of Hadlow *et al.* (1979, 1982) did not detect infectivity in CNS until 24 months of age.

The SSC further concluded that the choice of an upper age limit of 3 years might exclude over 99.5% of clinically-affected cattle from entering the food and animal feed chain. About 1 in 2000 of the clinical presentations might occur in cattle of 30 months or younger.

4.3.5. Elements of the risk assessment: rendering

In table 4 hereafter, a summary of the present knowledge on clearance factors is given for meat and bone meal derived from ruminant material, as well as information on the origin of the data and comments on the validity/exploitability of the data. *The industry and research institutions are invited to provide additional data, whenever available.*

Experimental data have demonstrated the TSE agents possess an unusual heat resistance as compared with "conventional" agents such as heat resistant spore forming bacteria.

According to Riedinger (1998a, 1998b), the evaluation of available experimental data from several experiments allows the conclusion that the thermal inactivation of TSE agents also follows a logarithmic pattern as nearly every decay process in natural science. The results of various investigations of show a flat inactivation curve within a temperature range up to 140 °C eventually resulting in a reduction of infectivity within a range of 6 to 9 log. Results from other rendering experiments (at least 133° C, /20 min/3 bar) have demonstrated a reduction of infectivity by heat/pressure treatment of at least 3 log (the initial titre was too low to detect a higher log reduction). Subsequent drying gives under practical conditions an additional reduction of 2 to 3 log as demonstrated by Taylor (1997). No rest infectivity could be detected in the resulting material. In most of these experiments scrapie strains were used but there are no indications that the BSE agent has a higher heat resistance than the scrapie agent. Even in a rendering experiment reflecting practical conditions, using large quantities of infected brain, the titre in the raw material didn't exceed $10^{3,1}$ ID 50/g measured in mice (in the Scrapie experiment). This can be considered as worst case conditions. From the above mentioned experiments it could be concluded that drying is sufficient for the elimination of the BSE agent, but since in these experiments the range of detectable infectivity was too small for extrapolation, and due to the necessary safety range of covering 5 to 6 log in an inactivation procedure, plus 2 to 3 log security range, more available data had to be evaluated from the existing literature to have a calculatory decision base .

Model calculations allow to conclude that temperature/pressure conditions at 133°C will reduce the TSE infectivity to a negligible level. Assuming an infectivity of 1 ID50 per 100 milligrams of infected brain and spinal cord, one bovine in a rendering batch of 10 tons would represent an infectivity of 20,000 ID50. Inactivation by temperature/pressure will reduce the level of infectivity by 3 logs. In addition, still according to Riedinger, drying will further reduce infectivity by 3 logs. This will result to 0.02 ID50 in the total batch, equivalent to about 1 case in 50 to 100 years when completely fed to ruminants. However, still according to Riedinger (1998a, 1998b), the really expected reduction of infectivity by heat/pressure treatment will be in a range of at least 5 to 6 logs and thus further reduce the risk of transmission, say to 0.0002 to 0.00002 ID50 in the total batch. From this it can be concluded that an epidemic is prevented.

Table 4: Clearance factors for meat-and-bone meal

Process	Literature references	TSE specific? (Yes/No)	Values (range)	TSE agent or strain	Recommended value (SSC)
Batch size:					
1 animal: possibly in one or several batches?			Offals from one animal may end up in several batches;		1 BSE bovine in batch of 10 tons
High temperature regime during an hyperbaric process	(1)	BSE	133°C/20 minutes: 1.7 $\log_{10}$		
	(2)	Scrapie	133°C/20 minutes: 3.1 $\log_{10}$		
	(3)	BSE	133°C/20 minutes: 2-3 $\log_{10}$		

and during a given period of time	(4)	Scrapie	121°C/60 minutes: 7.6 $\log_{10}$	Scr. 263 K ('82)	
	(5)		126°C/30 minutes: 2.1 $\log_{10}$ 126°C/60 minutes: 3.6 $\log_{10}$ 136°C/4 minutes PL: >5.6 $\log_{10}$	Scr. 22 A ('83)	
~~133°C/20'/3 bars~~ (batch processing)	(5)	Scrapie	126°C/30 minutes: 5.9 $\log_{10}$ 126°C/60 minutes: > 6.9 $\log_{10}$ 136°C/4 minutes PL: > 6.9 $\log_{10}$	Scr.139 A ('83)	At least 3 $\log_{10}$
	(6)	Scrapie	121°C/60 minutes: > 6 $\log_{10}$	Scr.263 K ('84)	
	(7)	Scrapie	121°C/60 minutes: > 8.3 $\log_{10}$ 132°C/60 minutes: > 8.8 $\log_{10}$	Scr. 263 K ('86)	
	(8)	Scrapie	134°C/30 minutes: 5.3 $\log_{10}$	Scr. 263 K ('90)	
	(9)	CJD	121°C/120 minutes: 4.2 $\log_{10}$ 132°C/30'; 60' :> 4.8 $\log_{10}$	CJD ('91)	
	(10)	Scrapie	121°C/60 minutes: 5.4 $\log_{10}$ 121°C/90 minutes: 5.7 $\log_{10}$ 132°C/60 minutes: 6.6 $\log_{10}$ 132°C/90 minutes: > 7.4 $\log_{10}$	Scr. 263 K ('93)	
(continuous processing)					

Table 4: Clearance factors for meat-and-bone meal (continued)

Process (continued)	Literature references	TSE specific? (Yes/No)	Values (range)	Comments	Recommended value (SSC)
Drying	(11)	Scrapie	2-3 $\log_{10}$	– Clearance will depend upon exact physical conditions – The effect of drying may not be fully additive to the clearance during rendering. – The drying process may result in a concentration of the possible residual infectivity	?
Process as a whole	Expert judgement			There is no guarantee that the successive clearance factors are additive	At least 3 $\log_{10}$
Dilution in feed					?
Dilution as					2 $\log_{10}$ for 1%

cross-contaminant					3 $\log_{10}$ for 0.1%

(1) Taylor, 1997
(9) Taguchi et al., 1991
(2) Taylor, 1997
(10) Ernst and Race, 1993
(3) Schreuder et al., 1998
(11) Taylor et al., 1997
(4) Brown et al., 1982
(5) Kimberlin et al., 1983
(6) Rohwer, 1984
(7) Brown et al., 1986
(8) Brown et al., 1990

Remark: The above table needs to be permanently updated so as to include future research results.

Riedinger (1998b) concludes that the process respecting the "133°C/20'/3 bars" conditions is safe enough with regard to a normal risk and gives moreover a sufficient security range. This means that separate treatment of SRM would not be necessary especially in regions with negligible and low risks if the material is treated in the above mentioned vapour pressure system.

Based on the data available in the literature, Casolari (1998) proposed the following theoretical model for prion inactivation as a function of temperature, in the framework of a non-exponential (N-EIK) kinetics of inactivation of efficacy in the sterilisation treatment:

"Time for prion destruction (minutes required to obtain 22D[3]) at different temperatures according to the N-EIK model.

Temperature (in ℃)	*120*	*125*	*130*	*135*	*140*	*145*	*150*	*155*
Min. time for 22 D	*393*	*77*	*21*	*6*	*2*	*0,6*	*0,2*	*0,06"*

He finally concludes, also based on an exponential (EIK) analysis of the inactivation factors, that *"The treatment applied in Europe for animal residues starting from April 1, 1997 [the "133°C/20'/3bars" condition] seems to be safe"*.

The Working Group noted and discussed in detail the approach concerning TSE agents and safe rendering procedures proposed by Casolari (1998) and Riedinger (1998a, b). The working group agreed that these approaches are consistent and logical. However, the Riedinger approach is based on the assumption that the BSE agent behaves basically similar to most microbes and viruses. The Working Group does not share these assumption and also questions whether, under practical industrial conditions, the infected tissues can be regarded as evenly distributed in the mass undergoing treatment. Given the uncertainties linked to the BSE agent the working group can not agree to the conclusion that a properly carried out batch process, applying the 133°C/20'/3 bar conditions, would result in a safe product (MBM), irrespective of the infectivity status of the starting material.

The working group further notes that in Casolari (1998) the evidence for differences between strains of agent in terms of their thermostability are ignored (Dickinson & Taylor, 1978; Kimberlin et al, 1983) and that some data from his calculations were excluded because they are considered too different from other data. Newer inactivation data (Taylor, 1998) have meanwhile also become available which do not support

[3] The D value represents the time needed to reduce infectivity levels by one log at a given temperature.

Casolari's conclusions. This confirms a previous observation that it is inappropriate (and potentially dangerous) to attempt to predict the effectiveness of new heat inactivation regimes for scrapie-like agents by simply extrapolating from existing heat -inactivation data (Taylor & Fernie, 1996). In general, the inactivation kinetics of conventional micro-organisms by steam is a first order (straight-line) reaction. Unfortunately, the inactivation kinetics of scrapie-like agents are often not of first order (straight line) nature (Taylor & Fernie, 1996).

Although recognising the fact that several researchers believe that, in the correct operating conditions, the infectivity reduction following pressure treatment can be even higher and reach 10^5-10^6, the members of the *ad hoc* working group established for meat and bone meals within the SSC have, for prudent reasons, thought it was indicated to consider a value of 10^3 (drying excluded) as shown in experiments by Taylor et al. (1997) and Schreuder (1998).

In batch processes, these conditions are expected to be realised for non-desiccated raw material with a particle size of maximum 50mm and with a lipid and water content that normally can be expected for animal tissues and where this water generates the steam during the rendering process. If the starting material is dry, and steam was injected during the process, the required time may have to be increased to allow heat to penetrate the particles of raw material so that equivalent infectivity reduction conditions are realised. However, any equivalent process should be evaluated and acknowledged on a case by case basis.

Regarding the fact whether these conditions should be realised under batch or continuous conditions, the Scientific Steering Committee is of the opinion that there will be no difference in the effectiveness provided the time / temperature / pressure parameters are effectively achieved in every part of the material being processed. The Working Group considers that for continuous processes, this equivalency still needs to be validated. In fact, because the highest-risk tissues (brain and spinal cord) are relatively soft and will tend to break up and disperse onto the surface of the more solid particles, the required time / temperature / pressure conditions may not necessarily be reached in every point of the bulk in operational plants which are working in continuous mode. Analytical systems should therefore be developed to monitor and experiments carried out to verify that the announced process conditions were really achieved in every part of a same batch in the autoclave, be it processed as a batch or under continuous conditions.

Remarks:

a. The working group notes that at a core temperature of 133°C, the corresponding pressure, if all air is evacuated, will be lower then 3 bars[4]. Since under practical conditions temperature, pressure and overall composition of the material (e.g. salt content) can only be measured with limited accuracy, a temperature of 133ºC is given here. The temperature / time combination should be realised with all air replaced by steam in the whole sterilisation chamber, which should be assured by technical means including continuous stirring and pre-cooking during at at least 100°C for at least 5

[4] Due to physical laws the temperature of 133ºC under steam pressure conditions corresponds to 2.95 bars.

minutes. Other temperature/time/pressure/particle size conditions could result in an equivalent inactivation, but should be evaluated on a case-by-case basis.

b. The Scientific Steering Committee further considers that the application of the "133ºC/20'/3 bars" standard as a post-sterilisation phase in stead of applying it during the production process itself, would result in an equivalent inactivation of a TSE agent provided the material contains enough water[5] to achieve the previously defined conditions. If not, steam-injection will have to be applied to achieve the required conditions. Because the average particle size of MBM is only around 2mm, re-hydration of, and penetration into, MBM duriong the autoclaving process is not considered to be problem.

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[5] Approximately 60%.

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