SCIENTIFIC OPINION

The safety of meat and bone meal from mammalian animals, naturally or experimentally susceptible to Transmissible Spongiform Encephalopathies.

Adopted by the Scientific Steering Committee at its meeting of 26-27 March 1998

Following a public consultation on the preliminary opinion adopted on 19-20 February 1998

(Version updated on 3.04.98:

see double underlined section in the summary table)

I. Report of the Working Group

1. Definition of meat and bone meal derived from mammalian animals.

- The definition and report hereafter do not refer to blood meal.
- For the purpose of the present report, meat and bone meal, derived from mammalian animals, is defined as processed animal protein intended for animal consumption, treated so as to render it suitable for direct use as a feeding stuff or as an ingredient in a feeding stuff for animals.
- In the frame of the present report, rendering means any processing of slaughter by-products (excluding pure blood), animals unfit for human consumption or of meat scraps for the production of meat and bone meal. The term "rendering" includes the collection of such materials and subjecting them to minimal processing, or distribute them to firms other than renderers whose intended use for the products may include animal feed. The term includes also blending animal protein products.

2. Background

a) 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; MAFF et al., 1997), the process conditions of 133°C during 20 minutes at 3 bar are confirmed 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) (....)"*

b) On 18 July 1996, the European Commission 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.

c) 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., J.Inf.Dis., 1990; Wright and Taylor, The Lancet, June 1993; Taylor et al., Veterinary Record, December 1995);*

- *the published works relate to experiments using limited volumes of material; hence the results cannot 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. (...) 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. (...)

d) When it adopted its opinion on Tallow on 8.09.97, the MDSC/SSC 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 infective 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."

e) 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 infective 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.

On the basis of what precedes, the MDSC/SSC decided during its meeting of 16 October 1997, to create a working group on the safety of Meat and Bone Meal. This report was prepared by that working group.

3. On the production of meat and bone meal

In order to express an opinion on the safety of meat and bone meal it is important to consider a number of aspects of the production conditions that may affect the safety of the end product.

3.1 Continuous or batch processing.

On the question which type of production process (batch or continuous) is the safest, it can reasonably be expected that no difference in the effectiveness will occur provided the time/temperature/pressure parameters required for inactivating or eliminating the TSE agent are effectively achieved in every part of a same batch during batch or continuous processes. The problem related to the industrial equipment is to ensure the reaching of the desired temperature in every point of the autoclave for the required time. Available data prove the significant reduction of infectivity only when treating batches at 133°C for 20 minutes and 3 bars of pressure. However, 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 or verify that the announced process conditions were really achieved in <u>every</u> part of a same batch in the autoclave, be it processed as a batch or

under continuous conditions. Equivalent processes should be evaluated and acknowledged on a case by case basis.

3.2 Meat and bone meal traces in ruminant feeds from cross-contamination

A majority of the enterprises producing feeds produce both monogastric and ruminants concentrates. Since ruminants concentrates are not always produced in dedicated lines, in most cases ruminant concentrates are up to today contaminated with MBM (microscopy evaluation and search of specific bone fragments - lower limit of individuation of 0.01% or less). The problem is not restricted to the production industries, but also to the transport system of raw materials and concentrate for ruminants (most of all concentrate in meal form).

Given the present production systems, a real zero presence level cannot be considered on scientific grounds. The implementation of good manufacturing practice (GMP) in several plants is reducing, even though not excluding, the risk of contamination of raw materials. It would therefore be useful to examine the possibility of fixing a maximum level of acceptance of proteins from mammalian material based on the sensitivity of the analytical method or on a precise definition. The risk analysis preliminary to defining tolerance limits should take into account, amongst others:

- the fact that the "133°C / 20 minutes / 3 bar" treatment imposed by the UE is in force since 1 April 1997;
- the fact that meat and bone meals are produced only from low risk materials;
- the infectious potential of different extraneural tissues, which may vary according to the animal species;
- the dose needed to infect an animal.

4. Some considerations regarding the safety of meat and bone meal

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

- The origin of the BSE epidemic in the UK is 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.
- 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 Scientific Steering Committee, rather limited. The experiment, because of its scope, size and duration, has not been repeated in other laboratories. Finally, the experimental rendering 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 are 100% safe, are available from operational rendering plants. 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 to 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 mice infection tests which 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 compromised 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 scrapie in mice is 100.000-fold (Kimberlin, 1996). Also, it has been calculated that the transmission of BSE to mice by the oral route is 200.000-fold less efficient than by intracerebral challenge (Kimberlin, 1994). 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 regard to any risk from infection by its consumption. On the other hand, however, certain strains of natural scrapie are transmitted as easy 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 (Dickingson and Taylor, 1978; Kimberlin et al., 1983). To date, however, there are no compelling data to indicate that BSE agent is 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.

4.2. The Working Group noted and discussed in detail the approach concerning TSE agents and safe rendering procedures proposed by Riedinger (1998a, b). The working group agreed that this approach is consistent and logic. However, it is based on the assumption that the BSE agent behaves basically similar to most microbes and viruses. The Working Group does not share this assumption. For this and other reasons 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.

Instead of a reduction factor of 10^{-5} to $^{-6}$ (drying excluded) as proposed in Riedinger (1998&, b, c), the working group recommends to assume a factor of 10^{-2} to $^{-3}$ (drying excluded) as shown in experiments by Taylor et al. (1997) and Schroeder (oral communication, unpublished).

II. OPINION

5. The question.

The SSC had to address the following 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?"

6. Scientific opinion

Introductory notes:

a) In its opinion of 22-23 January 1998 defining the BSE risk for specific geographical areas, the Scientific Steering Committee has listed the factors contributing to the incident and propagation risks in a geographical area. On 20 February 1998 the SSC adopted that list, slightly amended, as final opinion. More work needs to be done on the definition of risk regions or countries. The Committee is preparing a further opinion on the geographical aspects of BSE risks.

The four classes of the geographical aspect of BSE risks used in the opinion hereafter, are therefore indicative and, for the time being, are: "high risk countries", "lower risk countries", "countries considered free of BSE or classified as at negligible risk" and "Countries with an unknown TSE status". The corresponding wording of the opinion hereafter may thus possibly have to be revised / updated in accordance with the forthcoming Scientific Steering Committee opinion on the geographical aspects of TSE/BSE risks.

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

b) Notwithstanding the fact that the question put to it refers to the safety of meat and bone meal from mammalian animals, the Scientific Steering Committee the opinion below only covers MBM derived from ruminants possibly infected with BSE or scrapie.

c) The opinion hereafter does not address the issue of the intrinsic risks related to the practice of feeding back of animal derived feedingstuffs to the same or similar species.

Following the approval of the preceding report of the working group by the TSE/BSE ad-hoc group, the Scientific Steering Committee adopted the following opinion on the safety of meat and bone meal:

6.1. Definitions:

- *For the purpose of the present opinion meat and bone meal derived from mammalian animals are defined as processed animal protein intended for animal consumption which has been treated so as to render it suitable for direct use as a feeding stuff or as an ingredient in a feeding stuff for animals. Rendering means any processing of slaughter by-products, animals unfit for human consumption or meat scraps for the production of meat and bone meal. The term includes the collection of such materials and subject them to minimal processing, or distribute them to firms other than renderers whose intended use for the products may include animal feed. The term includes also blending animal protein products.*
- *The wording "Fit for human consumption" hereafter refers to material from animals that passed both pre- and post mortem inspection by an 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 Scientific Steering Committee stresses that positive identification of material not fit for human consumption should be possible, to avoid possible entering of such material in the food or feed chains.*
- *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.*
- *The wording "133°C/20'/3 bars" refers to production process conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. Regarding the fact whether they 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 <u>every</u> part of the material being processed. 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 drier, but steam was injected in the beginning of the production, the required temperature/time/pressure combination may have to be adjusted. For example, the temperature may have to be increased above 138°C so that equivalent infectivity reduction conditions are realised. However, any equivalent process should be evaluated and acknowledged on a case by case basis.

6.2. Concerning the raw material it has to be accepted that, as long as no test is available which allows to diagnose non-clinical BSE or scrapie cases (pre-mortem), the only way of determining that the basic raw material is of negligible risk, is a procedure of sourcing of the raw material.

6.3. The Scientific Steering Committee strongly recommends that manufacturers implement and respect HACCP[1] procedures. It is essential to identify and describe the hazards and critical points for the different processes utilised in production. Two of these points are certainly the traceability and treatment at the origin (e.g. removal of specified risk materials) of the raw material.

6.4. The sections of the opinion hereafter cover the approach to be followed if the risk of infectivity of meat and bone meal is to be reduced to the lowest possible level. In addition a more detailed risk analysis could be carried out to assess the exact level of the risk of infectivity for an animal. Such risk assessment would take account of:

- *the type of final product and infectivity reduction capacity of the production procedure;*
- *the geographical origin of the raw material;*
- *the type of raw material, including the age of the animals;*
- *the removal or not of specified risk materials;*
- *the incidence and propagation components of the BSE borne risk, as specified in the opinion of 22-23 January 1998 of the Scientific Steering Committee defining the BSE risk for specified geographical areas*

This assessment requires results of experiments on and justified estimates of, reduction factors during the various steps of the production process, from sourcing to marketing. Such data are not always available, as some experiments are still ongoing or only in a planning phase. In order to provide the Commission with two alternative choices, the Scientific Steering Committee will eventually complete the in this opinion followed approach to reduce the risk of infectivity in the final product to the lowest possible level with a quantitative risk analysis. The results of the latter analysis may eventually change or ask for an update of the recommendations hereafter.

6.5. Further criteria to be met in order to ensure a degree of safety of meat and bone meal from mammalian origin allowing it to be fed to non-ruminants.

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

Whether or not the source of the raw material can be 'considered free of a given TSE' must be the object of detailed evaluation by the appropriate independent expert bodies. As long as no tests are available which allow to diagnose non-

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clinical TSE cases (pre-or post-mortem), the only way to determine if the raw material is of negligible risk, is to determine the TSE status of the geographic origin of the material on the basis of an appropriate procedure using recognised criteria. Raw material from a source, satisfying the conditions for a TSE-free status, can be used without additional conditions regarding minimal production processes or removal of specified risk materials, provided it is also fit for human consumption. Nevertheless, the SSC recommends, as an additional precautionary measure to obtain the minimum level of risk and to stop any proliferation of infectivity of possible unknown origin, the submission of the material to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. This should prevent the building up of circulating TSE-agents as a result of sporadic spontaneous cases, even if these have not yet been shown to occur, also for these TSE-free countries.

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

The raw material has to originate from animals certified officially to be fit for human consumption. The material should be submitted to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. However, it cannot be excluded that under worst case conditions, traces of infectivity could remain. In order to minimise a possibly remaining risk of infectivity, specified risk materials shall be excluded from the production of meat and bone meal and other animal feed.

The SSC further recommends that measures are taken to avoid cross contamination between raw material from different animal species and between the final products to be consumed by different species.

The Scientific Steering Committee recognises that the fact of combining both the requirements of using animals that are fit for human consumption and of submitting the material to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents, may be perceived as too precautionary. Accepting that this combination of conditions should not necessarily become a general principle, the SSC nevertheless is of the opinion that reaching the maximum possible level of safety should be the objective, in order to prevent a possible build up of circulating TSE-agents in the animal population as a result of sporadic outbreaks of TSE, even if these have not yet been shown to occur. Whilst an additional submission to 133°C during 20 minutes at 3 bar of material already declared fit for human consumption and to be used as human food cannot realistically be envisaged, the manufacturing of meat and bone meal for animal consumption does accept such conditions. As the TSE transmission barrier between animals of a same species is lower than between animals used as food and humans, to prevent also for these countries the possible building up of circulating TSE-agents as a result of sporadic spontaneous cases, even if these have not yet been shown to occur, and more generally, because of the risk of microbiological contamination in rendering and processing plants, this combination of conditions increases the safety of the animal as human food.

6.5.3. *For high risk countries:*

As it cannot be excluded that under worst case conditions, traces of infectivity could remain despite of the all the possible safeguards put into place, the Scientific Steering Committee recommends that no meat and bone meal, to be used as feed for mammalian animals, should be produced from ruminant animals.

Note:

The Scientific Steering Committee considered but eventually rejected the following alternative option:

The raw material has to originate from animals certified by a competent veterinary authority to be fit for human consumption. The specified risk materials shall be excluded from the production of meat and bone meal and other animal feed. The material should be submitted to a production process respecting conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents. (However, under these process conditions, it cannot be excluded that under worst case conditions, traces of infectivity could remain.) The material should be sourced from animals that are young enough (below 12 months) to not represent any realistic risk of harbouring BSE or scrapie infectivity at detectable levels. Dedicated rendering plants and transports should be used, to avoid cross-contamination between raw material from different animal species and between the final products to be consumed by different species.

The above alternative was rejected because it was considered as not being realistic for practical reasons and because of the difficulties that would be encountered when monitoring and enforcing its implementation. However, the second alternative could be considered as an intermediate step for high risk countries but where the BSE epidemic is under control and which are in the process of becoming (lower) risk countries.

6.5.4. *Countries with an unknown BSE status should be evaluated individually on the basis of a detailed evaluation using appropriate criteria. If no judgement on the basis of available evidence or because of a lack of information is possible, they should be considered as high risk countries.*

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

6.6. *On the question whether the above specified production process conditions of 133°C during 20 minutes at 3 bar, or an equivalent process with demonstrated efficacy in terms of inactivating TSE agents, 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 necessary time/temperature/pressure parameters are effectively achieved in every part of the material being processed. The SSC further recommends that analytical systems are developed to monitor or 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. Equivalent processes should be evaluated and acknowledged on a case by case basis.*

6.7. *The Scientific Steering Committee finally stresses the urgent need of a study and risk analysis being carried out so as to possibly define acceptable tolerance*

limits of the possible content of impurities and proteins from mammalian material in feeds which theoretically should not contain any such impurity. A zero contamination level is indeed difficult -if not impossible- to achieve, also from a scientific point of view. To determine the content of impurities and proteins, an accepted standard analysis method would also be required."

Summary table: criteria to be met in order to ensure a degree of safety of meat and bone meal from mammalian origin allowing it to be fed to non-ruminants.

Geographical origin of the animals:	Criteria to be met:
BSE FREE or NEGLIGIBLE	- Material certified as being from area considered BSE free or at negligible risk. - Animals certified as fit for human consumption. - Production process respecting 133°C/20'/3 bars or equivalent in terms of inactivating/eliminating the BSE or scrapie agent. - Regarding batch or continuous processing: see section 3.1.
LOWER RISK	- Certified as fit for human consumption[2]. - Specified risk materials[3] excluded. - Production process respecting 133°C/20'/3 bars or equivalent in terms of inactivating/eliminating the BSE or scrapie agent; batch or continuous process. - Measures to avoid cross-contamination.
HIGH RISK	– No meat and bone meal, to be used as feed for mammalian animals, should be produced from ruminant animals.
STATUS UNKNOWN	To be evaluated; if no judgement on the basis of available evidence or because of a lack of information is possible: consider as high risk.[4]

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2 Fit for human consumption means here that the animal should comply with all the appropriate and relevant national and EU legislation.

3 The wording "SRMs or Specified risk materials" refers to all tissues listed in the opinion of the Scientific Steering Committee (SSC) adopted on 9 December 1997 and amended on 19-20 February 1998. However, the SSC intends to consider the possibility of making a selection of specified risk materials on the basis of the results of a risk assessment, which takes into account the geographical origin of the animals, their species and their age.

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

7. Not exhaustive list of scientific and technical documents used by the working group.

Anonymous, 1995. Bekanntmachung über die Zulassung und Registrierung von Arzneimitten + annexes. Reprint from Pharm.Ind., 57, 12, 261-270.

Bader,F., Davis, G., Dinowitz, B., Garfinkle, B., Harvey, J., Kozak, R, Lubiniecki, A.., Rubino, M., Schubert, D., Wiebe, M., Woollet, G. 1997. Assessment of Risk of Bovine Spongiform Encephalopathy in Pharmaceutical Products. Pharmaceutical Research and Manufactures of America (PhRMA) - BSE Committee. Technical document, Washington D.C. (USA). 58 pp

BGA (German federal health Office), 1994. BSE and Scrapie - German Federal health Office (BGA) on Safety Measures to be adopted for Medicinal Products. In: Drugs made in Germany, Vol.37 (N°2): pp 36-49.

Brown, P., Wolff, A., Liberski, P.P.,Gajdusek, D.C.,1990. Resistance of scrapie infectivity to steam autoclaving after formaldehyde fixation, and limited survival after ashing at 360°C: practical and theoretical implications. J.Infect.Dis. Vol.161: pp 467-472.

Bruce, M., Chree, A., McDonnell, I., Foster, J., Pearson, G., Fraser, H., 1994. Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier. Philosophical Transactions of the Royal Society

Detlev, R., Kellings K., Post, K., Wille, H., Serban, H., Groth, D., Baldwin, M.A., Prusiner, S.B., 1996. Disruption of Prion Rods Generates 10-nm Spherical Particles Having High Helical Content and Lacking Scrapie Infectivity. Journal of Virology, March 1996, Vol.70. (3):1714-1722

Dickinson, A.G., Outram, G.W., Taylor, D.M., Foster, J.D., 1989. Further evidence that scrapie agent has an independent genome. In: Unconventional virus diseases of the central nervous system. Paris 2-6 December 1986, pp 446-459. Edited by Court, L.A., et al., 1989. Fontenay-aux Roses (France).

Dickinson, A.G., Taylor, D.M., 1978. Resistance of scrapie agent to decontamination. New England Journal of medicine, Vol.299, pp. 1413-1414.

Dormont, D., 1998a. Letter of 20 January 1998 to the Scientific Steering Committee secretariat, regarding specified risk materials. (Original French version and its translation into English).

Dormont, D., 1998b. Letter of 17 February 1998 to the Scientific Steering Committee secretariat, regarding the safety of gelatine. (Original French version only).

Dormont, D., 1998c. Letter of 16 February 1998 to the Scientific Steering Committee secretariat, regarding the comments on the draft opinion on the safety of MBM. (Original French version only).

E.C. (European Commission), 1994. Report on detailed procedures for the validation of rendering processes adopted by the Scientific Veterinary Committee (Animal health Section) on 12 December 1994.

E.C. (European Commission), 1996a. The Scientific Veterinary Committee. Opinion of 9 April 1996 on the risk associated with certain animal products in relation to Bovine Spongiform Encephalopathy (BSE).

E.C. (European Commission), 1996b. The Scientific Veterinary Committee. Opinion of 18 April 1996 on the results of the rendering study Phase II - Scrapie.

E.C. (European Commission), 1996c. The Scientific Veterinary Committee. Report on the Control of risks from BSE- and Scrapie-infected material in regard to protection of public and animal health. Adopted on 21 October 1996.

E.C. (European Commission), 1997a. Rapport de la Conférence Scientifique Internationale sur les Farines Animales. Bruxelles, 1 & 2 juillet 1997.

E.C. (European Commission), 1997b. Opinions on the safety of tallow and of tallow derivatives, adopted by the Multidisciplinary Scientific Committee / Scientific Steering Committee on 8 September 1997.

Eleni, C., Di Guardo, G., Agrimi, U., 1997. Encefalopatia Spongiforme Bovina (BSE): Analisi del Rischio in Italia. Large Animals Review, Vol.3 (N°4): pp. 5-15.

EMEA (The European Agency for the Evaluation of Medicinal Products), 1997. Revised draft 14 - rev.1 (2nd September 1997) of the Committee for Proprietary Medicinal Products (CPMP) Note for guidance on minimising the risk of transmitting animal Spongiform Encephalopathy agents via medicinal products.

Kimberlin, R.H., 1994. Presentation in: Transmissible Spongiform Encephalopathies: a consultation with the Scientific Veterinary Committee of the European Communities. Brussels, 14-15 September 1993. Kluwer Academics. Dordrecht, p. 455**.**

Kimberlin R.H., 1996. Bovine spongiform encephalopathy and public health: some problems and solutions in assessing the risks. In:**Court, L. and Dodet, B., Eds., 1996.** Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Proceedings of the IIIrd International Symposium on Transmissible Subacute Spongiform Encephalopathies: Prion Diseases. Elsevier, Paris, 16 pages.

Lasmézas, C.I., Deslys, J.-P., Demaimay, R., Adjou, K.T., Hauw, J.-J., Dormont., D., 1996. Strain specific and common pathogenesis events in murine models of scrapie and bovine spongiform encephalopathy. Journal of General Virology, Vol.77: pp 1601-1609.

MAFF (Ministry of Agriculture and Fisheries, UK), IAH (Institute of Animal Health), Prosper De Mulder, CNEVA (France), 1997. Inactivation of the BSE and scrapie agents during the rendering process. Final report of the Study contract N° 8001 CT90 0033 co-funded by the European Commission and MAFF.

OIE (Office International des Epizooties), 1997. Bovine Spongiform Encephalopathy (BSE). Chapter 3.2.13 of the OIE International Zoo-Sanitary Code on BSE.

Prusiner, S.B., 1997. Prion Diseases and the BSE Crisis. Science, Vol. 278 (10 October 1997): pp 245-251.

République Française, 1996. Comité Interministriel sur les Encéphalopathies Subaiguës Spongiformes Transmissibles. Réponses aux questions du Directeur Général de la Santé, du Directeur Général de l'Alimentation et du Directeur

Général de la Consommation, de la Concurrence et de la Dépression des Fraudes, adressées au Comité en juillet 1996.

Riedinger, O., 1998a. Stellungnahme zum vorläufigen Arbeitspapier der "BSE/TSE-working group", das unter Federführung van Prof.Piva am 12.02.98 in Brüssel beraten soll. Discussion paper. 10pp (available in German and in English).

Riedinger, O., 1998b. Additional remarks concerning TSE agents and safe rendering procedure. Letter of 19 March 1998 to the SSC secretariat.

Robinson, M.M., Hadlow, W.J., Huff, T.P., Wells, G.A., Dawson, M., Marsh, R.F., Gorham, J.R., 1994. Experimental infection of mink with bovine spongiform encephalopathy. Journal of General Virology, Vol.75, pp.2151-2155.

Taylor, D., 1997. Current science on inactivation of TSE. (Extract from a public presentation).

Taylor, D., 1998. Letter to the secretariat of the SSC of 13.3.98 responding to comments on the draft opinion of the SSC on the safety of MBM.

Taylor, D.M., Fraser, H., McConnell, I., Brown, D.A., Brown, K.L., Lamza, K.A., Smith, G.R.A., 1994. Decontamination studies with the agents of bovine spongiform encephalopathy and scrapie. Arch. of Virol., Vol. 139: pp. 313 - 326.

Taylor, D.M., Woodgate, S.L., Atkinson, M.J., 1995. Inactivation of the bovine spongiform encephalopathy agent by rendering procedures. Veterinary Record, Vol.137: pp.605-610.

Taylor, D.M., Woodgate, S.L., Fleetwood, A.J., Cawthorne, R.J.G., 1997. The effect of rendering procedures on scrapie agent. Veterinary Record. Vol.141, pp. 643-649.

Vanbelle, M., 1997. The scientific aspects of the safety of Meat and Bone Meals: how to ensure food security and that of the animals. Presentation at the International Meat and Bone Meal Conference, Brussels, 1-2 July 1997.

WHO (World health Organisation), 1995. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies. Geneva, 17-19 May 1995. Document WHO/CDS/VPH/95.145

WHO (World health Organisation), 1996. Report of a WHO consultation on public health issues related to human & animal transmissible spongiform encephalopathies.(With the participation of FAO and OIE) Geneva, 2-3 April 1996. Document WHO/EMC/DIS/96.147.

WHO (World health Organisation), 1997. Report of a WHO consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies.(With the participation of the Office International des Epizootie, OIE) Geneva, 24-26 March 1997.

Wilesmith, J.W., Wells, G.A.J., Cranwell, M.P., Ryan, J.B.M., 1988. Bovine spongiform encephalopathy: epidemiological studies. Vet.Rec., Vol.123: pp.638-644.

Wilesmith, J.W., Ryan, J.B., Atkinson M.J., 1991. Bovine spongiform encephalopathy: epidemiological studies on the origin. Vet.Rec., Vol.128, pp.199-203..

Woodgate, S., 1997. TSE Agents: Inactivation by rendering systems and the role of inactivation research on new processing regulations for the European rendering industry. Conference paper. Lipidex 97: 18-21 March 1997 Symposium 1 Tradefair. Antwerp (B). also attached to COLIPA, 1997).