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# **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 Epizooties (OIE)**

**Geneva, Switzerland  
24-26 March 1997**



**WORLD HEALTH ORGANIZATION**

**Consultation jointly organized by the Biologicals Unit, the Blood Safety Unit, and the Division of Emerging and other Communicable Diseases Surveillance and Control in collaboration with the Neuroscience and Food Safety Units.**

*World Health Organization, 1997*

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## OPENING REMARKS

On 20 March 1996, the national health authorities in the United Kingdom noted the occurrence of 10 human cases of a new and previously unreported form of Creutzfeldt-Jakob disease (CJD). While no scientific evidence of a link could yet be established, the hypothesis was put forward that these cases might be associated with exposure to the agent that causes bovine spongiform encephalopathy (BSE)<sup>1</sup>. Consumers reacted to this announcement with deep concern, and there was a major loss of confidence and disruption of trade in cattle and bovine products from the United Kingdom and other countries in which BSE had been reported. These events raised many urgent questions about the safety of animal-derived products and by-products entering the food chain or being used in medicine.

Since 1991, the World Health Organization (WHO) has convened five scientific consultations on public health issues related to animal and human transmissible spongiform encephalopathies (TSE) to evaluate the most up to date information at the time of each consultation. Medicinal products containing bovine tissues were thoroughly dealt with in 1991<sup>2</sup> and later consultations in 1993<sup>3</sup>, 1995<sup>4</sup> and 1996<sup>5-6</sup> dealt mainly with products entering the human food chain, especially meat, milk, gelatin and tallow.

In order to update the preventive measures proposed in 1991 to minimize the risks associated with the use of medicinal products and medical devices containing bovine derived materials, a meeting of international experts was convened at WHO in Geneva on 24-26 March 1997 to review recent insights into the molecular nature of the agent, methods for agent and disease detection and the latest developments in removal and inactivation of TSE infectivity.

The Consultation was opened by Dr H. Nakajima, Director-General of WHO. He recalled that at the time of the meeting WHO had been notified of 15 definite cases of the new variant CJD (nvCJD) in the United Kingdom, and one in France, and that recently published data give further support to the hypothesis that these cases are a consequence of human exposure to the BSE agent. He noted that modelling techniques have been used to assess the epidemiological data, but that insufficient information is available at present to make any well-founded prediction about the future number of nvCJD cases. Dr Nakajima indicated that the objectives of the Consultation were to evaluate the potential risks associated with medicinal products and medical devices containing bovine derived and also human derived materials. Although the Consultation mainly focused on medicinal products in relation to animal and human TSEs, an update of measures to minimise risks related to food products from ruminant origin were also considered.

Dr C. Masters (Australia), Dr J. Löwer (Germany) and Dr R. Rohwer (USA) were chairpersons of the consultation and Dr M. Pocchiari (Italy) and Dr B. Hörnlimann (Switzerland) were nominated rapporteurs. The list of participants is attached as Annex 3.

## **1. BACKGROUND INFORMATION ON TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSEs)<sup>a</sup>**

### **1.1 Epidemiology and clinical features of Creutzfeldt-Jakob disease (CJD)**

CJD is a rare and fatal human neurodegenerative condition. Like other TSEs, CJD is experimentally transmissible to animals and a characteristic spongiform change is seen on neuropathology. Epidemiological studies indicate a worldwide occurrence with a relatively constant incidence of approximately 1 case/million/year. CJD occurs as a sporadic disease in about 85% of cases, 10-15% are inherited and the remaining cases are iatrogenic.

The cause of sporadic CJD remains unknown despite extensive study, and, in particular, there is no evidence of a causal link with scrapie, a naturally occurring TSE of sheep and goats. The condition usually occurs between the age of 50 and 75 years and has an average age of death of about 65 years. Characteristically the patient develops a rapidly progressive dementia associated with multi focal neurological signs, ataxia, and myoclonus. The electroencephalogram (EEG) shows a characteristic pattern (generalised 1-2Hz triphasic periodic complexes) in the majority of cases but other routine laboratory tests and cerebral imaging are normal or show non-specific abnormalities only. A recently described assay to detect the 14-3-3 protein in the cerebrospinal fluid is claimed to have a high sensitivity and specificity but it has not yet been widely evaluated. No treatment has been shown to convincingly slow the illness progression and death occurs within a year of onset in 90% of cases. Although in the correct clinical context a characteristic EEG recording is considered diagnostic, confirmation of the diagnosis of CJD relies on neuropathological examination. Familial disease, also experimentally transmissible, is inherited as an autosomal dominant trait associated with an abnormality of the prion protein (PrP) gene. Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI) are similar inherited transmissible neurodegenerative disorders.

Iatrogenic CJD has arisen following the use of contaminated human pituitary-derived growth hormone (94 cases) or gonadotropin (4 cases), dura mater grafts (69 cases), corneal transplantation (3 cases), neurosurgical instruments (4 cases) and stereotactic EEG electrodes (2 cases)<sup>b</sup>. The problem associated with human pituitary derived growth hormone and the availability of the alternative rDNA derived product has led to the discontinuation of the pituitary derived material virtually worldwide. The increasing number of reported iatrogenic CJD cases associated with dura mater grafts raises similar concerns, especially when used in neurosurgery. Dura mater is the tough collagenous membrane that forms the outer sheath surrounding the brain and spinal cord and can therefore be considered to be a material in a high risk category related to CJD. Human cadaveric-derived dural homografts have been used in surgical procedures since the late 1950's, particularly for neurosurgical conditions, including head trauma, cranial and spinal tumours and repair of congenital malformations. They have also been used in

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<sup>a</sup> This section has been prepared by the WHO Secretariat in close collaboration with the chairs and rapporteurs of the consultation

<sup>b</sup> The number of all the iatrogenic cases were kindly provided by Dr Paul Brown (May 1997)

general and paediatric surgery for large defects of the abdominal wall, and in maxillofacial procedures. In 1987 the first case of CJD linked with the use of cadaveric-derived dural homograft during a neurosurgical procedure was reported and subsequently a further 68 cases are known to have occurred. However, the introduction in the late 1980's of a decontamination procedure involving treatment with 1 N sodium hydroxide for 1 hour<sup>7</sup> and rigorous donor selection should have reduced the risk of transmitting CJD via dura mater graft.

The clinical phenotype and incubation period of iatrogenic disease is related to the route of agent inoculation: central infection leads to a pattern of illness akin to sporadic CJD about 18 months post exposure whereas peripheral inoculation is associated with a progressive cerebellar syndrome following an average incubation period of about 12 years. Kuru, a human TSE thought to be transmitted via ritualistic cannibalism, shares similar clinical features with peripherally inoculated iatrogenic CJD and is known to have an incubation period ranging from 4.5 to over 35 years.

## **1.2 Bovine spongiform encephalopathy (BSE)**

BSE was first reported in British cattle in November 1986. Current evidence suggests that the disease originated from the use of feed supplements containing meat and bone meal (MBM) contaminated by a TSE agent. The stringency of the rendering process by which animal materials are converted to MBM and tallow changed in the early 1980's and a decreased use of hydrocarbon solvents and the adoption of lower temperatures may have resulted in increased survival of the infective agent. The British Government made BSE notifiable in June 1988 and shortly afterwards a statutory ban on the feeding of ruminant-derived protein to ruminants was introduced. In 1989 a ban on the use of specified bovine offals for human consumption was enforced. BSE infectivity has been demonstrated in the brain, spinal cord and retina of naturally affected cattle and also in the distal ileum of those infected experimentally. However, a wide range of bovine tissues from clinically affected cases of BSE have shown no detectable infectivity using the mouse bioassay, and these include muscle, milk and a range of lymphoreticular tissues. Although these results are reassuring, the decrease in transmissibility to mice due to the bovine/murine "species barrier" is not well known and may differ from that between bovines and humans. The incidence of BSE has continued to decline rapidly since 1992, almost certainly in response to statutory measures. Although the pattern of the epidemic remains consistent with the hypothesis that the vast majority of cases arose by infection with contaminated feed, it remains possible that other routes of transmission may occur infrequently, in particular maternal transmission from dam to calf. The BSE agent is also thought to have been responsible for the occurrence of novel spongiform encephalopathies in domestic cats and captive animals, mostly in the United Kingdom. BSE has recently been experimentally transmitted via the oral route to sheep but no evidence exists of natural transmission. However concern over this possibility led to a ban on the use of ovine brain and spinal cord for human consumption in the UK and France. By the end of 1996, over 168 000 confirmed cases of BSE had been reported in United Kingdom. Relatively small numbers of cases have also been reported in native cattle in Switzerland, the Republic of Ireland, France, Portugal and the Netherlands. Small number of cases have also been reported in Germany, Italy, Oman, Canada, Denmark, and the

Falkland Islands, but solely in animals imported from the UK (cases reported by the Office International des Epizooties).

### **1.3 The nature of the agent**

The nature of the transmissible agent of the TSEs remains the subject of much debate. Many scientists believe it is composed entirely of a self replicating isoform of a normal cellular membrane protein - the protein only or 'prion hypothesis. Others believe the agent is viral-like and contains nucleic acid. The identification of multiple 'strains of agent, with characteristic incubation periods and distribution of neuropathology when transmitted to mice, would be very much in keeping with the latter theory. However, increasing evidence is being accumulated in support of the prion hypothesis, including the co-purification of PrP with infection and the development of spontaneous central nervous system degeneration, indistinguishable from experimental murine scrapie, in transgenic mice following the introduction of the codon 101 point mutation (corresponding in mice to the GSS-related mutation at codon 102) into the PrP gene. It is clear that the agent, whatever its exact nature, possesses a high degree of resistance to many conventional inactivation procedures, including ultraviolet and ionising irradiation, extremes of temperatures, ethanol, formaldehyde and standard autoclaving.

### **1.4 New variant Creutzfeldt-Jakob disease (nvCJD)**

In March 1996, 10 cases of a new variant of CJD were reported in the United Kingdom. These unusually young patients exhibited an apparently novel and distinct clinicopathological phenotype and it was concluded that their disease was most likely associated with exposure to the BSE agent, probably with an incubation period of between 5 and 10 years. In April 1996 the recent death of a young man from nvCJD was reported from France and by March 1997 a further five definite and one probable case of nvCJD had been identified in the UK. The hypothesis of a causal link with BSE is supported by the presence of pathological features similar to nvCJD in macaques inoculated with BSE, and by the demonstration that nvCJD is associated with a molecular marker that distinguishes it from other forms of CJD and which resembles that seen in BSE, and BSE transmitted to a number of other species. Furthermore, intensive CJD surveillance in 5 European countries, with a low potential exposure to the BSE agent, failed to identify any additional cases of nvCJD. The link between nvCJD and BSE remains unproven and it is only possible to speculate on any potential route of transmission in those cases identified to date. However, analysis does not indicate that medicinal products or occupational exposure were likely sources of infection in the majority of these cases. Proof of any association between BSE and nvCJD may depend on the results of ongoing transmission studies to ascertain the degree of strain similarity of the agents, and continued epidemiological vigilance in the UK, Europe and the rest of the world.

Knowledge of the human and animal TSEs has increased dramatically in the past decade. However, the great concern engendered by the possible association of nvCJD with BSE demonstrates the paramount importance of further intensive research in this

field. Firstly there is a need to more clearly understand the exact nature of the causative agent; secondly to identify new and clinically useful diagnostic tests; and finally to consider the possibility of therapeutic interventions.

## **2. Conclusions and Recommendations of the Consultation**

### **2.1 Measures to minimize risks to human from medicinal products and medical devices derived from bovine material**

On the basis of current scientific knowledge about the agents causing BSE and other animal TSEs, the group stressed that the ideal situation would be to avoid the use of bovine materials in the manufacture of medicinal products, as well as the use of materials from other animal species in which TSEs naturally occur. In practice, this may not always be feasible and, in this case, careful selection of source materials is the best way to secure maximum safety of active substances, excipients and reagents. Therefore the epidemiological status of BSE in countries and herds should be taken into consideration by manufacturers of medicinal products wishing to procure raw material of bovine origin. Depending upon the information available on the source and type of material used, additional measures may be required to reduce further the potential risk of contamination. These include controlling the collection of bovine materials and the introduction of procedures to inactivate or remove possible BSE contamination. Other factors which need to be taken into consideration are the amount of material administered and the route of administration. Consideration should also be given to the risk to benefit ratio of the medicinal product.

#### **2.1.1 Selection of source materials of bovine origin**

Careful selection of source materials is the most important criterion for the safety of medicinal products. Activities of veterinary services should be designed to control the disease in cattle; to evaluate those control activities in countries where it is present; and, in countries where BSE is absent, to avoid the occurrence of the disease and to establish appropriate surveillance systems for early detection. Detailed guidelines covering these aspects are issued by the Office International des Epizooties (Chapter 3.2.13, Bovine Spongiform Encephalopathy, of the OIE code). The group strongly recommended that OIE documents currently in force be consulted.

It was agreed that the most satisfactory source of materials is from countries which have not reported indigenous cases of BSE and have a compulsory BSE notification system, compulsory clinical and laboratory verification of suspected cases and a surveillance program. Also, it should be ensured that there is no risk of BSE infection from the following factors: importation of cattle from countries where a high incidence of BSE has occurred nor the importation of the progeny of affected cows. In addition, it should be ensured that meat-and-bone meal containing any ruminant protein originating from countries with a high or low incidence of BSE (as classified by OIE) is

being avoided in ruminant feed.

Materials may also be sourced from countries where a low number of indigenous cases have occurred, if in addition to the factors set out in the previous paragraph, the carcasses of all infected animals are destroyed, the progeny of affected cows are not used, the feeding to ruminants of ruminant derived protein (other than milk) is banned. In some countries the feeding to ruminants of all mammalian derived protein is banned because of the difficulty in identifying the animal source of the protein.

The use of source materials from countries where there is a high incidence of BSE is usually not acceptable. However, even in those countries, it may be acceptable to collect materials for specific products from well monitored herds, where evidence is provided that the herds had no cases of BSE, had never been fed mammalian derived protein (other than milk), had a fully documented breeding history, and had introduced new genetic material only from herds with the same BSE-free status.

### **2.1.2 Type of bovine material**

Although it is now known that the distribution of detectable infectivity in BSE affected cattle appears to be much more restricted than that found in sheep naturally affected by scrapie, it is prudent at the present time to keep the classification of tissues and body fluids shown in the table (see Annex 1) for the selection of source materials. As can be seen in this table, the maximum infectivity titres of tissues from Suffolk sheep and goats, measured intracerebrally in mice<sup>8-9</sup> at the clinical stage of natural scrapie, have been classified on the basis of relative infectivity titres, and, following a decreasing order, into four categories - from category I (high infectivity) to category IV (no detectable infectivity within the limits of the bioassay using mice injected intracerebrally).

For practical purposes, other considerations should also influence the classification of bovine tissues according to their potential risk. As an example, all of the bovine intestines, from duodenum to rectum, should be included in category II, even though corresponding ovine tissues (ileum, proximal colon, distal colon) were found to have different scrapie titres. Since scrapie infectivity in the adrenal gland was found to be higher in goats than sheep, the adrenal gland has been moved to category II.

Cell lines known to be capable of concentrating or amplifying agents causing TSEs should not be used in the manufacture of medicinal products, apart from reasoned exceptional cases.

The information currently available suggests that, given assurances of adequate collection and/or processing, certain derivatives of materials in category IV are unlikely to present any risk of contamination. These include for example lactose, casein, wool alcohols and lanolin.

The group concluded that the raw material used for the production of gelatin should be sourced from safe materials. In addition, a manufacturing process utilizing production conditions which have been demonstrated to significantly remove or inactivate TSE infectivity in source tissues should be used. If this is done, gelatin is considered safe for all purposes.

### **2.1.3 Conditions under which materials are collected**

It is recognized that the potential risks will be influenced by circumstances under which tissues are removed. For example, the contamination of some tissues might be increased if infected animals are slaughtered by penetrative brain stunning or if the brain and/or spinal cord is sawed.

Body fluids should be collected with minimal damage to tissue, and cellular components should be removed. Foetal blood (category IV) should be collected without contamination from other maternal or foetal tissues including placenta, amniotic and allantoic fluids.

When cross contamination of a source tissue with a tissue within a higher risk category cannot be reasonably excluded, the higher risk tissue must be assumed for evaluation purposes. For example, bone material from the skull and vertebrae (excluding tail vertebrae) should be considered at higher risk compared to other bones because it is unlikely that brain and spinal cord are completely removed. Any risk from central nervous tissue attached to skulls or vertebrae can be reduced by excluding these bones from source materials.

### **2.1.4 Procedures capable of reducing or removing infectivity**

Processes that remove or inactivate infectivity and, in particular a combination of these procedures, complement the safety provided by sourcing. Manufacturers should consider including such procedures in their manufacturing processes. Where claims are made that the production process makes a significant contribution to the safety of the product the process should be validated.

The group concluded that the raw material used for the production of tallow should be sourced from safe materials. Materials derived from tallow (for example, triglycerides, glycerol, sorbitan esters, etc.) that have been subjected to highly rigorous processes of extraction and purification are considered unlikely to be contaminated.

### **2.1.5 Amount of bovine material**

In evaluating the potential risk of infecting humans with the BSE agent, it is logical to consider the amount of bovine material of whatever type in the dose administered to humans. Multiple exposures increase the opportunity for infection. Particular attention should be paid to implants and medical devices where the "exposure time" may be very long.

### **2.1.6 Route of administration**

The hypothetical risk of transmission of BSE to humans by medicinal products

will be influenced considerably by the route of administration. Data obtained from studies of experimental scrapie in mice show that direct injection into the CNS is the most efficient route of infection. Among the non-neural routes, the intravenous route is the most efficient (although less than intracerebral), followed by intraperitoneal and then intramuscular or subcutaneous injection. The oral route is less efficient than the parenteral routes.

### **2.1.7 Comments**

The potential risks associated with a given medicinal product administered to humans should be considered on a case-by-case basis, taking into account all the foregoing factors, and the benefits to patients.

These recommendations apply to all medicinal products where active substances, excipients and reagents derived from bovine tissues are used during their production processes. Although the recommendations relate particularly to materials of bovine origin, the same principles should also be applied to materials used in the manufacture of medicinal products when these are obtained from sheep, goats and other species naturally affected with TSEs.

These measures should also be followed by the manufacturers of cosmetic products.

## **2.2 Measures to minimize risks to humans from human derived material**

The transmission of TSEs is most efficient when there is no species barrier, when material is deposited directly into the brain and when the material is brain, spinal cord or related tissue, potentially containing high titres of infectivity.

### **2.2.1 The risk of transmission of CJD by contaminated instruments, pituitary hormones and dura mater**

CJD has been transmitted by contaminated instruments in the course of neurosurgery. The group strongly recommended that instruments used for neurosurgical and invasive ophthalmological procedures on patients with CJD be discarded. If instruments are to be re-used, they should be immersed in 1 N NaOH for one hour, cleaned, and then autoclaved at 134C for one hour.

Hormones purified from human pituitary glands (growth hormone and gonadotropin) have resulted in the transmission of CJD. Therefore, these hormones should not be sourced from human pituitary glands.

Because over 50 cases of CJD have resulted from cadaveric dura mater grafts, the group strongly recommended that dura mater no longer be used, especially in the case of neurosurgery, unless no alternative is available. If dura mater is to be used, only material which is from non-pooled sources originating from carefully screened donors, and

subjected to validated inactivation treatment should be considered.

CJD is known to have been transmitted on three occasions by a corneal transplant. Since there are no alternatives to corneal transplants, corneal donors should be carefully selected and all collecting equipment effectively cleaned and disinfected.

### **2.2.2 The risk of transmission of CJD by blood and blood products**

Though there is no proven or even probable instance of transmission of CJD by blood, blood components or plasma derivatives, increased awareness has raised concern about such a possibility. Laboratory studies have sought to determine whether or not the infective agent may be present in blood or blood products from diseased individuals. Epidemiological studies have sought to determine whether or not disease transmission has actually occurred.

Numerous attempts have been made by several different laboratories during the past 20 years to detect the infective agent in the blood of experimentally infected animals. Although some results have been negative, several laboratories have reported the irregular presence of small amounts of infectivity in blood and particularly in buffy coat during both the preclinical incubation period and clinical phase of the disease. A recent experiment has demonstrated a low level of infectivity in the plasma and cryoprecipitate fraction from mice experimentally infected with CJD. A few attempts have also been made to detect the infectious agent in the blood of humans with CJD. Four instances have been reported (one from serum and three from buffy coat). It is important to emphasize that the presence of the infectious agent in the blood of either experimentally infected animals or naturally infected humans has been determined by transmission of disease to laboratory rodents only by intracerebral inoculation, and that the single experiment using an intravenous route of inoculation failed to transmit disease (units of blood from 3 CJD patients transfused into 3 chimpanzees).

Taken together, these data suggest that blood components from patients with CJD may contain low levels of infectivity. However, it is considered difficult to extrapolate from experimental data to the situation in a medical setting. Furthermore, epidemiological studies have yet to identify a single instance in which disease was actually transmitted by blood.

Published case control studies have not found an elevated risk of CJD following transfusion. However, case control studies designed specifically to determine the risk from transfusion have not been completed. It is reassuring that in a population highly exposed to specific blood products, as is the case of haemophiliacs, there are no reports of CJD to date. Surveillance in this population should continue. Cohort studies of the recipients of products derived from blood donors subsequently diagnosed with CJD have been recently initiated. No cases of CJD have been reported, but statistically significant data are not yet available. While published epidemiologic studies give some reassurances that transmission of CJD has not occurred through blood, they are limited in scope, and improved surveillance for CJD is essential.

The recent appearance of a nvCJD warrants special mention. Most of the laboratory and epidemiological studies of blood infectivity and disease transmissibility

have been made on the sporadic form of CJD, and clinical and neuropathological observations suggest that nvCJD may have distinctive biological features. Further studies of new variant cases are needed in order to determine whether or not the tissue distribution of infectivity in nvCJD differs from that of classical CJD, and, in particular, whether the infectious agent might be present in blood more frequently or in greater amounts than in the blood of patients with other forms of CJD.

On the basis of current scientific knowledge the groups, listed below, identified as being at increased risk of developing a TSE, should be permanently excluded from blood donation. Therefore, in addition to routine internationally recognised donor selection criteria, which already effectively exclude individuals suffering from CJD, GSS, FFI or dementia from making donations, the following donors should be excluded:

donors who have been treated with extracts derived from human pituitary glands (growth hormone and gonadotropin) donors who have a familial history of CJD, GSS or FFI donors who have received a human dura mater graft Inevitably individuals with CJD who have donated blood prior to the development of clinical symptoms will be identified. Countries have formulated appropriate policies for the management of plasma products derived from plasma pools thus implicated. The group recognises the different stances currently applied by regulatory authorities in different countries. Batches of plasma derivatives withdrawn in one country should not be exported to another country.

### **2.3. Minimizing risks related to food products from ruminant origin**

The group recommended that all countries should conduct a BSE risk assessment and develop a risk management strategy, taking into account the need to significantly reduce or eliminate TSE infectivity in ruminant-feeds, the effectiveness of rendering processes, the problems in controlling the hazards from bovine tissue and need for effective surveillance of the disease. If the result is to establish laws aimed at the protection of animal and/or public health, the group emphasized the need for this law to be vigorously enforced and shown to be enforced.

The group recommended harmonized global surveillance for TSE with special emphasis to CJD and BSE. In addition, further investigations concerning BSE transmission within species, e.g. from cattle to cattle were recommended.

#### **2.3.1 Safety of milk**

The WHO Consultation of 2-3 April 1996 concluded that milk and milk products were safe. This statement was based on unsuccessful attempts to transmit the agent from cows clinically affected by BSE by inoculation of their milk into mice by intracerebral or intraperitoneal route or by feeding milk.

More recent data from a suckler herd study in the UK further support the conclusions concerning the safety of milk. No BSE cases out of 132 offspring born to BSE-infected cows have occurred so far (minimum age was 20 months in August 1996).

The present Consultation concurs with the view that milk is safe. Further consideration should be given to maternally associated risks including the significance of colostrum.

### **2.3.2 Risk of BSE occurring in sheep**

Sheep can be experimentally infected parenterally or orally with a small quantity of BSE infected brain. In contrast to experimental BSE in cattle, in which detectable infectivity is limited to the CNS, the retina and the distal ileum, BSE-infected sheep also harbour infectivity in spleen, and (when further tissues will have been tested) may prove to have an even wider tissue distribution similar to scrapie. There is as yet no evidence that BSE has been established in sheep populations, but it has been observed that experimentally transmitted BSE in sheep broadly has the same clinical features as natural scrapie. Concern has therefore been expressed that if BSE occurs in sheep in the fields it could be mistaken clinically for scrapie.

Since 1996 legislation has been enacted in some countries to include certain sheep and goat tissues that might contain high titres of BSE infectivity in the list of tissues that are excluded from the human and animal food chains.

In countries where sheep and goats may have been exposed to ruminant protein potentially contaminated with the BSE agent, the risk of BSE occurring in sheep and goats should be assessed and appropriate legislative measures should be taken when necessary.

### **2.3.3 Gelatin in the food chain**

Please refer to section 2.2 last paragraph and 2.3 last paragraph.

## ANNEX 1

### CATEGORIES OF INFECTIVITY IN BOVINE TISSUES AND BODY FLUID

(Based on relative scrapie infectivity of tissues and body fluids from naturally infected suffolk sheep and goats with clinical scrapie)

CATEGORY I High infectivity	Brain, spinal cord, (eye)*
CATEGORY II Medium infectivity	Spleen, tonsil, lymph nodes, ileum, proximal colon, cerebrospinal fluid, pituitary gland, adrenal gland, (dura mater, pineal gland, placenta, distal colon)
CATEGORY III Low infectivity	Peripheral nerves, nasal mucosa, thymus, bone marrow, liver, lung, pancreas
CATEGORY IV No detectable infectivity	Skeletal muscle, heart, mammary gland, milk, blood clot, serum, faeces, kidney, thyroid, salivary gland, saliva, ovary, uterus, testis, seminal testis, foetal tissue, (colostrum, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine).

\*Tissues in brackets were not titrated in the original studies (8,9) but relative infectivity is indicated by other data on spongiform encephalopathies.

## ANNEX 2

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## ANNEX 3

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