Memoranda/Mémorandums

Medicinal and other products and human and animal transmissible spongiform encephalopathies: Memorandum from a WHO meeting*

The report in March 1996 of 10 human cases of a novel form of Creutzfeldt–Jakob disease in the United Kingdom, and its possible link to the agent that causes bovine spongiform encephalopathy (BSE), raises many questions about the safety of animal-derived products and by-products entering the food chain or being used in medicine. This Memorandum updates the preventive measures put forward in 1991 to minimize the risks associated with the use of bovine-derived materials in medicinal products and medical devices.

Introduction

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 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) (7). 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 as well as in other countries where bovine spongiform encephalopathy (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, WHO has convened five scientific consultations on public health issues related to animal and human transmissible spongiform encephalopathies (TSEs) 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 (2), and later consultations in 1993 (3), 1995 (4), and 1996 (5, 6) 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 findings on the molecular nature of the agent, methods for agent and disease detection, and the latest developments in removal and inactivation of TSE infectivity.

Epidemiology and clinical features of Creutzfeldt–Jakob disease

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

The cause of sporadic CJD remains unknown despite extensive study, and, in particular, there is no

* This Memorandum is based on the report of a WHO Consultation (unpublished document WHO/EMC/ZOO/97.3; WHO/BLG/97.2) held in Geneva on 24–26 March 1997. A list of participants is given on p. 513.

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evidence of a causal link with scrapie, a naturally occurring TSE of sheep and goats. The condition usually occurs between 50 and 75 years of age and the average age of death is about 65 years. Characteristically the patient develops a rapidly progressive dementia associated with multifocal neurological signs, ataxia, and myoclonus. The electroencephalogram (EEG) shows a characteristic pattern (generalized 1–2 Hz 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 convincingly shown to slow the illness’s progression and death occurs within a year of onset in 90% of cases. Although in the correct clinical context a characteristic EEG pattern 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 disease (GSS) and fatal familial insomnia (FFI) are similar, inherited transmissible neurodegenerative disorders.

Iatrogenic CJD has occurred 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) (P. Brown, unpublished data, May 1997). 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 use of 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 with respect to CJD transmission. Human cadaveric-derived dural homografts have been used in surgical procedures since the late 1950s, particularly in neurosurgical conditions, including head trauma, cranial and spinal tumours, and repair of congenital malformations. Such homografts have also been used in general and paediatric surgery for large defects of the abdominal wall, and in maxillofacial procedures. In 1987 the first case of CJD linked to 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 1980s of a decontamination procedure involving treatment with 1 mol/l sodium hydroxide solution for 1 hour (7) and rigorous donor selection should have reduced the risk of transmitting CJD via dura mater grafts.

The clinical phenotype and incubation period of iatrogenic CJD 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 has an incubation period ranging from 4.5 years to over 35 years.

**Bovine spongiform encephalopathy**

BSE was first reported in November 1986 in British cattle. Current evidence suggests that the disease originated from the use of feed supplements containing meat and bone meal (MBM) that was contaminated by a TSE agent. In the early 1980s the stringency of the rendering process by which animal materials are converted to MBM and tallow changed and the decreased use of hydrocarbon solvents and adoption of lower temperatures may have increased survival of the infective agent. The United Kingdom Government made BSE a notifiable disease 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 because of 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 from 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. Also, 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 United Kingdom 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, Ireland, France, the Netherlands, and Portugal. Small numbers of cases have also been reported in Germany, Italy, Oman, Canada, Denmark, and the Falkland Islands, but solely among animals imported from the United Kingdom (cases reported by the Office International des Epizooties).

**Nature of the transmissible agent**

The nature of the transmissible agent of the TSEs remains the subject of much debate. Many workers believe it is composed entirely of a self-replicating isofrom of a normal cellular membrane protein — the protein-only or "prion hypothesis". Others believe the agent is virus-like and contains nucleic acid. Identification of multiple "strains" of the agent, with characteristic incubation periods and distribution of neuropathology when transmitted to mice, would be consistent with the latter hypothesis. However, increasing evidence is being accumulated in support of the prion hypothesis, including the copurification 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 ionizing irradiation, extremes of temperatures, ethanol, formaldehyde, and standard autoclaving.

**New variant Creutzfeldt–Jakob disease**

In March 1996, 10 cases of a new variant of CJD (nvCJD) 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 5–10 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 cases and one probable case of nvCJD had been identified in the United Kingdom. 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 transmitted to a number of other species. Furthermore, intensive CJD surveillance in five European countries with a low potential exposure to the BSE agent has failed to identify any additional cases of nvCJD. The link between nvCJD and BSE remains unproven, however, and it is only possible to speculate on any potential route of transmission in those cases identified to date. Nevertheless, analysis does not indicate that medicinal products or occupational exposure are 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 among the agents and on continued epidemiological vigilance in the United Kingdom 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 between nvCJD and BSE demonstrates the paramount importance of further intensive research in this field. First, there is a need to understand more clearly the exact nature of the causative agent; second, to identify new and clinically useful diagnostic tests; and last, to consider the possibility of therapeutic interventions.

**Conclusions and recommendations**

**Measures to minimize risks to humans 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 Consultation 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 pro-
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cure 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 that 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: benefit ratio of the medicinal product.

**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 BSE 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 (OIE). The Consultation strongly recommended that OIE documents currently in force be consulted.

The most satisfactory source of materials is from countries that have not reported indigenous cases of BSE and which have a compulsory BSE notification system, compulsory clinical and laboratory verification of suspected cases, and a surveillance programme. Also, it should be ensured that there is no risk of BSE infection from importation of cattle from countries where a high incidence of BSE has occurred or from the importation of the progeny of affected cows. In addition, it should be ensured that MBM containing any ruminant protein originating from countries with a high or low incidence of BSE (as classified by OIE) be avoided in ruminant feed.

Materials may also be sourced from countries where a low number of indigenous BSE 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, and 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 its animal source.

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 have had no cases of BSE, have never been fed mammalian-derived protein (other than milk), have a fully documented breeding history, and have had new genetic material introduced only from herds with the same BSE-free status.

**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 in sheep naturally affected by scrapie, it is prudent at present to use the classification of tissues and body fluids shown in Table 1 for selecting source materials. As shown in Table 1, the maximum infectivity titres of tissues from Suffolk sheep and goats, measured intracerebrally in mice (8, 9) at the clinical stage of natural scrapie, have been classified on the basis of relative infectivity titres 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. For 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) have different scrapie titres. Since scrapie infectivity in the adrenal gland is higher in goats than sheep, this 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 Consultation 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 that have been demonstrated to remove significantly or inactivate TSE infectivity in source tissues should be used. If this is done, gelatin is considered safe for all purposes.

**Conditions under which materials are collected.** Potential risks are influenced by the circumstances.

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*a OIE code, chapter 3.2.13. Available from Office International des Epizooties, 12 rue de Prony, 75017 Paris, France.
Table 1: Categories of BSE infectivity in bovine tissues and body fluid

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I (high infectivity)</td>
<td>Brain, spinal cord, (eye)*</td>
</tr>
<tr>
<td>II (Medium infectivity)</td>
<td>Spleen, tonsil, lymph nodes, ileum, proximal colon, cerebrospinal fluid, pituitary gland, and adrenal gland, (dura mater, pineal gland, placenta, and distal colon)</td>
</tr>
<tr>
<td>III (low infectivity)</td>
<td>Peripheral nerves, nasal mucosa, thymus, bone marrow, liver, lung, and pancreas</td>
</tr>
<tr>
<td>IV (no detectable infectivity)</td>
<td>Skeletal muscle, heart, mammary gland, milk, blood clot, serum, faeces, kidney, thyroid, salivary gland, saliva, ovary, uterus, testis, seminal testis, and fetal tissue, (colostrum, bile, bone, cartilaginous tissue, connective tissue, hair, skin, and urine)</td>
</tr>
</tbody>
</table>

* Based on relative scrapie infectivity of tissues and body fluids from naturally infected Suffolk sheep and goats with clinical scrapie.

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

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 sawn.

Body fluids should be collected with minimal damage to tissue, and cellular components should be removed. Fetal blood (category IV) should be collected without contamination from other maternal or fetal tissues, including placenta, amniotic, and amniotic 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 to be at higher risk than other bones because it is unlikely that brain and spinal cord have been completely removed. Any risk from central nervous tissue attached to skulls or vertebrae can be reduced by excluding such bones from source materials.

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 Consultation 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.

Amount of bovine material. In evaluations of 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.

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 central nervous system (CNS) is the most efficient route of infection. Among the non-neural routes, the intravenous is the most efficient (although less than intracerebral), followed by intraperitoneal, intramuscular, and subcutaneous injection. The oral route is less efficient than the parenteral routes.

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 the 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 obtained from sheep, goats, and other species naturally affected with TSEs.

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

Measures to minimize risks to humans from human-derived material

Transmission of TSEs is most efficient when there is no species barrier, when material is deposited di-
rectly into the brain, and when the material is brain, spinal cord or related tissue, which potentially contains high titres of infectivity.

**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 Consultation 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 mol/l sodium hydroxide solution for 1 hour, cleaned, and then autoclaved at 134 °C for 1 hour.

Hormones purified from human pituitary glands (growth hormone and gonadotropin) have transmitted 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, it was strongly recommended that dura mater no longer be used, especially for neurosurgery, unless no other alternative is available. If, nevertheless, dura mater is to be used, only material should be considered that is from non-pooled sources originating from carefully screened donors and subjected to validated inactivation treatment.

CJD has 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.

**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 over 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 CJD. A recent experiment has demonstrated a low level of infectivity in the plasma and cryoprecipitate fraction from mice experimentally infected with CJD. Also, a few attempts have 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 by intracerebral inoculation only, and that the single experiment using intravenous inoculation failed to transmit the disease (units of blood from three CJD patients transfused into three 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 blood transfusion; however, such 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 for 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 recently been initiated; no cases of CJD have been reported, but statistically significant data are not yet available. While published epidemiological studies give some reassurance 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 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 the new variant cases are needed to determine whether or not the tissue distribution of infectivity in nvCJD differs from that of classic 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 knowledge, the groups listed below, identified as being at an increased risk of developing a TSE, should be permanently excluded from donating blood. Therefore, in addition to routine internationally recognized donor
selection criteria, which already effectively exclude individuals suffering from CJD, GSS, FFI or dementia from making donations, the following groups 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; and
— donors who have received a human dura mater graft

Inevitably, individuals with CJD will be identified who have donated blood prior to developing clinical symptoms. Countries have formulated appropriate policies for the management of plasma products derived from plasma pools thus implicated. The Consultation recognizes the various stances currently applied by regulatory authorities in different countries. Batches of plasma derivatives withdrawn in one country should not be exported to another country.

Minimizing risks related to food products of ruminant origin

The Consultation recommended that all countries conduct a BSE risk assessment and develop a risk management strategy, taking into account the following: the need to reduce significantly or eliminate TSE infectivity in ruminant feeds; the effectiveness of rendering processes; the problems in controlling hazards from bovine tissue; and the need for effective surveillance of the disease. If the result is the establishment of laws aimed at protecting animal and/or public health, such laws should be vigorously and visibly enforced.

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

Safety of milk. A WHO Consultation of 2–3 April 1996 concluded that milk and milk products were safe (10). This statement was based on unsuccessful attempts to transmit the agent from cows clinically affected by BSE by intracerebral or intraperitoneal inoculation of their milk into mice or by feeding mice the milk.

More recent data from a suckler herd study in the United Kingdom further support these conclusions on the safety of milk: no BSE cases have occurred so far among 132 offspring born to BSE-infected cows (minimum age, 20 months in August 1996).

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

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 the spleen, and 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 has broadly the same broad clinical features as natural scrapie. Concern has therefore been expressed that if BSE occurs in flocks of sheep it could be mistaken clinically for scrapie.

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

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

Résumé

Produits médicaux et autres concernés par les encéphalopathies spongiformes transmissibles humaines et animales

Cette réunion avait pour objectif principal de mettre à jour les mesures proposées par la Consultation OMS organisée en 1991, visant à la réduction des risques associés à l’usage de produits médicaux contenant des tissus d’origine bovine. La Consultation a passé en revue les données épidémiologiques actuelles concernant la maladie de Creutzfeldt-Jakob (MCJ), les autres encéphalopathies spongiformes transmissibles humaines (EST), la nouvelle variante de MCJ (nvMCJ), l’encéphalopathie spongiforme bovine (ESB), ainsi que les différentes théories sur la nature de l’agent responsable. La Consultation a souligné, sur la base des connaissances actuelles, que l’idéal serait d’éviter l’utilisation des produits d’origine bovine pour la fabrication des produits médicaux, comme
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celle de matériel provenant d'autres espèces animales chez lesquelles des EST naturelles ont été rapportées. Il a été constaté qu'une telle éviction n'est en pratique pas toujours possible, et la Consultation a rappelé l'importance de la sélection minutieuse, quant à leur origine, des tissus et organes utilisés afin d'assurer une sécurité d'emploi maximale des principes actifs, des excipients et des réactifs. Les modalités de sélection et de classification des tissus et organes d'origine bovine en fonction de la quantité décelable d'agent de l’ESB sont précisées dans le rapport, de même que l'influence des conditions de leur collecte, des méthodes de réduction et d'élimination de l'agent, de la quantité de matériel bovin et de la voie d'administration. Les produits de base utilisés pour la production de gélatine doivent provenir de sources sûres. De plus ils doivent être soumis à un procédé qui a démontré sa capacité à éliminer l'agent qui pourrait s'y trouver, ou tout au moins une partie importante de celui-ci. Cette règle respectée, la gélatine est considérée comme sûre d'emploi, quelle que soit son utilisation.

La Consultation s'est aussi intéressée aux risques de transmission de la MCJ associés à l'utilisation d'instruments contaminés et à l'utilisation de certains produits médicinaux contenant des extraits et tissus d'origine humaine, tels que les hormones pituitaires et la dure-mère. Il a été recommandé que les hormones extraites de glandes pituitaires humaines et que la dure-mère d'origine cadavérique ne soient plus utilisées. La recommandation concernant la dure-mère doit être particulièrement suivie en neurochirurgie, hormis si aucune autre possibilité n'existe. Dans ce dernier cas les conditions de son utilisation ont été définies dans le rapport. Le risque de transmission par le sang et les produits dérivés a été évalué sur la base des données épidémio-logicociques et expérimentales existantes, y compris des résultats préliminaires des expériences les plus récentes. Ces dernières ont révélé que certaines fractions et éléments constitutifs du sang pouvaient contenir l'agent à des niveaux faibles. Il convient de noter que ces expériences ont été réalisées uniquement par injection intracérébrale, à des sous de laboratoire, de fractions du sang de souris infectées expérimentalement par la MCJ, et d'éléments du sang provenant de cas humains avérés de MCJ. Prises dans leur ensemble ces données expérimentales récentes suggèrent que les éléments constitutifs du sang de patients affectés de MCJ pourraient contenir de faibles quantités d'agent. Il est cependant difficile d'extrapoler à partir de ces données ce qui pourrait survenir dans la réalité de l'environnement médical. Les données épidémiologiques n’ont pas permis d'identifier un seul cas où la transmission par le sang a été prouvée. De plus, les études cas-témoins publiées donnent quelque réassurance que la MCJ n’a pas été transmise par le sang; elles sont toutefois d’une portée limitée et une surveillance accrue de la MCJ s'impose. Il a été recommandé que certains groupes identifiés comme à risque accru (les individus traités avec des extraits de glandes pituitaires, ceux qui ont des antécédents familiaux de MCJ, IFF et syndrome de GSS, ceux qui ont reçu un implant de dure-mère) soient exclus de manière permanente et définitive du don de sang. Les données cliniques et neuropathologiques suggérant que la nvMCJ a des caractéristiques biologiques distinctes des formes classiques de la MCJ, il est recommandé d’étudier plus avant la distribution tissulaire de l'agent responsable de la nvMCJ, et en particulier de déterminer si cet agent pourrait se trouver plus fréquemment ou en plus grande quantité dans le sang des patients infectés de nvMCJ que pour les autres formes de MCJ. La Consultation prenant en compte les données récemment publiées s’est finalement intéressée à certains produits alimentaires d'origine bovine, en particulier le lait. On a repris en la réaffirmant la conclusion de mai 1996, à savoir que le lait est sûr d'emploi, et souligné en outre le besoin d'étudier plus avant les risques d'origine maternelle, et en particulier le rôle du colostrum. Dans les pays où les moutons et les chèvres pourraient avoir été exposés par leur alimentation à l’agent de l’ESB, on a recommandé que le risque d’apparition de l’ESB au sein de ces troupeaux soit évalué, et que les mesures réglementaires appropriées soient mises en place lorsque jugé nécessaire.

References


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