

Distr. General

**WHO Guidelines on
Transmissible Spongiform Encephalopathies
in relation to
Biological and Pharmaceutical Products**



**World Health Organization
Geneva**



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Transmissible Spongiform Encephalopathies
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Blood Safety and Clinical Technology Department
Health Technology and Pharmaceutical Cluster
World Health Organization
Geneva



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1. INTRODUCTION

The appearance of a variant form of human Creutzfeldt-Jakob Disease (CJD) in the mid-1990s, as a result of the bovine spongiform encephalopathy (BSE) epidemic in the United Kingdom (UK), has increased the profile of transmissible spongiform encephalopathies (TSEs) as a risk to human health and has already affected public health policy worldwide. It is assumed that variant CJD (vCJD) results from the consumption of meat products from cattle infected with the BSE agent.

Policies developed to reduce the risks resulting from the hazard of vCJD and its potential for human-to-human transmission are based on three main factors: a) an unknown number of individuals might be infected with the BSE agent; b) the pathological misfolded prion protein (and infectivity detected by bioassay) is present in some peripheral tissues of patients who died of vCJD; c) blood of rodents, monkeys and sheep infected with TSE agents has transmitted disease experimentally. There is increasing concern about the possibility that vaccines, blood products and other pharmaceutical products—products that contain or were manufactured using bovine-derived or human-derived materials—might spread the agent of vCJD worldwide, even in countries where BSE has not yet been reported. There is, therefore, a need to ensure that regulatory authorities worldwide have reliable information to assess risk and evaluate product safety, so that steps can be taken to prevent the transmission of TSE to humans via biological and other pharmaceutical products.

In order to update the preventive measures proposed by the World Health Organization (WHO) in 1997 to minimize the risks associated with the use of vaccines, blood products and other pharmaceutical products containing bovine-derived and human-derived materials, a meeting of international experts was convened at WHO in Geneva on 3-5 February 2003. The purpose was to review the latest available data on the epidemiology, antemortem and postmortem diagnosis, detection of the infectious agents, and distribution of infectivity in tissues or body fluids of relevant species with TSEs.

Dr A. Asamoah-Baah, Executive Director Health Technology and Pharmaceuticals of WHO opened the Consultation. Dr Asamoah-Baah indicated that the objectives of the Consultation were to provide evidence-based information to regulatory authorities of Member States, especially to those where BSE has not yet been reported, with regard to risk assessment and precautionary and control measures for biological and pharmaceutical products. An additional goal was to promote harmonization of international regulations worldwide related to TSE.

This Consultation complements other important efforts of WHO in the follow-up of the scientific and epidemiological developments in TSEs such as the Joint WHO/FAO/OIE Technical Consultation on BSE held in 2001 (<http://www.who.int/csr/resources/publications/bse>) and the activities of the “Working Group on International Reference Materials for Diagnosis and Study of TSEs”, established in 1999 (<http://www.who.int/biologicals>), as a scientific forum to advance development of diagnostic tests based on available research methods.

Professor W. van Aken was nominated chairperson of the consultation and Dr D. Asher and Professor M. Pocchiari were nominated rapporteurs. A list of participants is annexed.

2. REVIEW OF SCIENTIFIC DEVELOPMENTS

Major scientific developments have occurred in the field of TSEs during the last 5 years. These include a better knowledge of the epidemiology of sporadic CJD (sCJD) and vCJD and an improved diagnostic criteria for sCJD and vCJD. Changes in the distribution and size of the BSE epidemic in Europe and elsewhere have been observed. The distribution of infectivity in tissues and body fluids in sCJD, vCJD, BSE and scrapie has been better established and the detection of the pathological misfolded prion protein (PrP^{TSE})¹ in different tissues has improved.

2.1 Epidemiology, clinical features and diagnostic criteria of 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 microscopic examination of the brain. Epidemiological studies indicate a worldwide occurrence of sporadic disease of approximately 1-2 cases per million people per year. Globally, over 80% of cases of CJD occur as a sporadic disease (sCJD). Familial, iatrogenic, and variant forms of CJD show much lower and variable incidence in different countries. Most cases of vCJD have been found in the UK.

The cause of sCJD 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, or with BSE. Most sCJD cases occur in persons between the age of 60 and 80 years with an average age at death of about 67 years. Characteristically the patient with sCJD develops a rapidly progressive dementia associated with multifocal neurological signs, ataxia, and myoclonus. Although, in the correct clinical context, a characteristic EEG recording and/or the detection of 14-3-3 protein in the cerebrospinal fluid are considered diagnostic, confirmation of the diagnosis of CJD still relies on neuropathological examination. The clinical and pathological features of sCJD are variable, and are influenced by a naturally occurring polymorphism at codon 129 of the gene encoding the prion protein (*PRNP* gene). A novel test based upon the detection of PrP^{TSE} in the nasal olfactory mucosa may improve the diagnosis of sCJD, but this test has not yet been evaluated in living patients.

Familial CJD, also experimentally transmissible, is expressed as an autosomal dominant trait associated with an abnormality of the *PRNP* gene. Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI) are similarly inherited transmissible neurodegenerative disorders.

There are now 313 cases² of iatrogenic CJD following the use of contaminated human pituitary-derived growth hormone (163 cases) or gonadotropin (4 cases), dura mater grafts (136 cases), corneal transplants (at least 3 possible cases), neurosurgical instruments (5 cases) and a stereotactic cortical-probe EEG electrode (2 cases). No new class of products causing iatrogenic CJD has been identified during the last 5 years, although the number of cases from past exposure to known products continues to increase.

¹ Because of increasing complexity in terminology for various forms of the prion protein (PrP), the consultation used the term PrP^{TSE} for all abnormal misfolded PrP associated with TSEs.

² The numbers of all iatrogenic cases were kindly provided by Dr Paul Brown (March 2003)

As of January 2003, 130 cases of vCJD were reported in the UK, 6 in France, and one each in the Republic of Ireland, Italy, USA and Canada. The Irish, US and Canadian patients had spent several years in the UK between 1980 and 1996, and were probably exposed to the BSE agent there, while the Italian and French cases had no history of travel outside their home countries. The median age at onset of vCJD is 26 years (range 12-74 years) with a median duration of illness of 14 months (range 6-39 months). Although a definite diagnosis of vCJD requires neuropathological examination, clinical and laboratory criteria have been established for the diagnosis of probable vCJD in living patients. All tested vCJD cases (121 worldwide) were homozygous for methionine at codon 129 of the *PRNP* gene. A distinctive feature of vCJD—in contrast to sCJD—is the frequent occurrence of PrP^{TSE} in lymphoid tissues (tonsil, spleen, lymph node, appendix). In 3 patients who had undergone appendectomy before onset of vCJD, two had immunoreactive PrP^{TSE} in lymphoid follicles of the appendix at 8 months and 2 years prior to death. One appendix was negative for PrP^{TSE} 9 years prior to death.

The causal link between vCJD and BSE is based on epidemiological, biochemical and transmission studies. The Joint WHO/FAO/OIE Technical Consultation on BSE (2001) reached a scientific consensus that BSE-contaminated food is the main avenue of exposure. Bovines, bovine products and by-products potentially carrying the BSE agent have been traded worldwide, giving this risk a global dimension. Epidemiological analysis does not indicate that medicinal products, blood and blood-derived products, or occupational exposure have been sources of infection in vCJD cases identified to date.

2.2 Bovine spongiform encephalopathy (BSE) and scrapie

BSE was first identified 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 with a TSE agent (probably from scrapie-infected carcasses). By the end of 2002, over 182,000 confirmed cases of BSE had been reported in the UK. Smaller outbreaks have been reported in native-born cattle in most other Western and Central European countries and in Israel and Japan (totalling 3822 cases reported to the OIE as of April 2003). Most recent cases were in clinically unremarkable animals recognized at the abattoir following the introduction of a statutory test for PrP^{TSE} applied after 1999 by member States of the European Union (EU) and by Switzerland to the brainstems of healthy cattle older than 30 months and suspect cattle at increased risk of BSE (fallen stock and other animals older than 24 months sent for casualty slaughter). The increase in recognized cases presumably resulted from better detection of infected animals during the pre-clinical and early clinical stages of illness rather than a true “second wave” of BSE. In the UK the incidence of BSE has continued to decline rapidly since 1992, almost certainly in response to a statutory ruminant feed ban introduced in 1988. This is consistent with the hypothesis that cases arose by infection from contaminated feed. Although epidemics of BSE in other European countries have been recognized more recently than that of the UK, most are also in decline, and, so far, no single country except the UK has recognized more than 1500 cases.

BSE infectivity has been demonstrated in the brain, spinal cord and retina of naturally affected cattle and also in the dorsal root ganglia, trigeminal ganglia, distal ileum (during incubation) and bone marrow (during clinical illness only) of those infected experimentally by the oral route. A wide range of other tissues (including most lymphoreticular tissues) from cattle sick with BSE—both naturally and experimentally acquired—showed no detectable infectivity using the mouse bioassay; parallel bioassays in cattle (now nearly complete) so far support the conclusion that there is a limited distribution of BSE infectivity in bovine tissues. BSE has been

experimentally transmitted via the oral route to sheep and goats, but there is still no evidence that these small ruminants have been naturally infected. However, concern over this possibility has led to increased efforts at active and passive surveillance of scrapie in the EU, based on the observation that experimental BSE in small ruminants resembles scrapie. Recently, infectivity was found in blood of sheep with natural scrapie and in blood of sheep with experimental BSE during both clinical illness and pre-symptomatic periods.

2.3 Diagnosis

The formation of PrP^{TSE} occurs only in TSEs and therefore its detection serves as a surrogate for detection of infectivity in biological samples. After experimental inoculation of rodents with TSE agents, PrP^{TSE} is, like infectivity, usually detectable in the central nervous system (CNS) many weeks before the appearance of overt disease, and its level increases during clinical illness. While the increase in PrP^{TSE} generally parallels that of infectivity, the precise relationship between PrP^{TSE} and infectivity is unclear. However, there are exceptions; under specific experimental conditions, the brain of TSE-affected rodents may be infectious (by bioassay) while PrP^{TSE} remains undetected. From the perspective of pre-clinical diagnosis, both the sensitivity of diagnostic methods and procedures to concentrate PrP^{TSE} are crucial, because the amount of PrP^{TSE} outside the CNS is likely to be extremely small, particularly in circulating blood. Concentration of PrP^{TSE} can be realized by chemico-physical precipitation, affinity chromatography or affinity precipitation techniques. Moreover, it has been reported that the amount of PrP^{TSE} in dilute solutions can be increased at least 10 to 20-fold by the “protein misfolding cyclic amplification” (PMCA) technique, potentially allowing improved detection of extremely small amounts of infected material. A recent report described the presence of an abnormal species of PrP in urine of CJD patients and animals with natural or experimental TSEs. Another study demonstrated PrP^{TSE} and infectivity in the skeletal muscle of mice experimentally infected with laboratory strains of TSE (something not found in natural TSEs). These potentially important studies have yet to be confirmed by other laboratories.

Among immunological methods for PrP^{TSE} detection, western blotting is the most thoroughly characterized and widely used method. It offers the advantage of recognizing different forms of PrP^{TSE} through the analysis of the molecular mass and the relative abundance of di-, mono- and non-glycosylated bands. These parameters characterize the so-called PrP glycotype, a kind of “PrP signature” that varies among different forms of TSE. PrP^{TSE} glycotyping has been proposed for distinguishing various forms of TSE (e.g., scrapie from BSE and sCJD from vCJD) and for improving the classification of human TSEs.

The latest generation of immunoassays are claimed to detect PrP^{TSE} in samples containing less than 1 LD₅₀ of BSE infectivity as measured by bioassay in transgenic mice expressing bovine PrP. Several ELISA and western blot methods are commercially available as ready-to-use kits, and have been validated in a study by the European Commission as screening tests for BSE in slaughtered cattle (so-called “rapid tests”). EC-approved immunoassays have also detected PrP^{TSE} in the brains of BSE-infected cattle at least 3 months before onset of clinical illness. However, no immunological method has yet proven sufficiently sensitive to detect PrP^{TSE} in the blood of infected humans.

3. RECOMMENDATIONS OF THE CONSULTATION

3.1 Tissue infectivity

The foundation of any attempt to construct a rational analysis of TSE risk from biological and pharmaceutical products must begin with an evaluation of infectivity in the human or animal tissues from which these products are derived. Although straightforward in principle, the task is complicated by differences in the timing of first appearance and final tissue distribution of infectivity in different species and diseases, by differences in the sensitivity of bioassay methods, and by incomplete data about infectivity levels in various tissues of interest. Tables IA, IB and IC in the Annex summarize current data about the distribution of infectivity and PrP^{TSE} in humans with vCJD and other human forms of TSE, in cattle with BSE, and in sheep and goats with scrapie. In general, it can be said that, paradoxically, whereas infectivity (PrP^{TSE}) in cattle with BSE has a more limited tissue distribution than in any other animal or human form of TSE, infectivity (PrP^{TSE}) in vCJD has a wider distribution than in other forms of human CJD.

3.2 Measures to minimize risks to humans from biological and pharmaceutical products in which bovine, ovine or caprine materials are used during manufacture

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 any biological or pharmaceutical product, as well as the use of materials from other animal species in which TSEs naturally occur. In practice, this is not always feasible, in which case a risk assessment should be performed. The risk assessment should take into account: a) the source of starting materials used as active substances, excipients or reagents and their potential infectivity; b) the possibility of cross contamination where starting materials are collected and processed; and c) the production processes for seed and other materials. The TSE risk assessment contributes to the overall risk-benefit analysis of biological and other pharmaceutical products.

3.2.1 Source of starting materials

Careful selection of the source of ruminant starting materials to be used to manufacture active substances, excipients and reagents is an important criterion in the TSE risk assessment. It was agreed that the most satisfactory source of materials is from countries where the risk of BSE in cattle is absent or low. Countries are encouraged to assess geographic BSE risk, and the Office International des Epizooties (OIE)—the world organization for animal health (oi@oi.int)—offers guidance in that process. The Geographical BSE Risk (GBR) categorization (risk of BSE for cattle in countries submitting requests) has been expanded and updated continuously by the Scientific Steering Committee (European Commission, Health and Consumer Protection Directorate General): http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html; that important activity will be continued by its successor, the European Food Safety Authority (EFSA).

The use of starting materials from countries with a high risk of BSE is usually not acceptable. However, even in those countries, the collection of starting materials for the manufacture of specific products from well-monitored herds may sometimes be allowed. This may be done after evidence is provided that the herds have had no cases of BSE, have an active surveillance programme, have never been fed mammalian-derived protein (other than milk), have a fully documented breeding history, and have introduced new genetic material only from herds with the same BSE-free status.

The age of an animal from which tissues or fluids are collected as starting materials may also be taken into account, since data are now available on the infectivity of tissues collected during the incubation period of experimental BSE. In general, tissues of younger animals contain less infectivity than those of older animals.

3.2.2 Tissue removal and processing

It is recognized that potential TSE risks might be influenced by circumstances under which tissues are removed. For example, slaughter of infected animals by penetrative brain stunning or sawing the skull or spinal column increase the risk that tissues containing little or no infectivity will be contaminated with higher-risk tissues. Body fluids should be collected with minimal damage to tissue, and cellular components should be removed. Fetal blood should be collected without contamination from other maternal or fetal tissues including placenta, amniotic fluid and allantoic fluid. Whenever possible, single-use instruments should be used for collection of tissues and fluids. When potential cross contamination of a source tissue with a tissue of higher-risk cannot be reasonably excluded, a higher risk of infection must be assumed for purposes of risk evaluation.

Facilities that provide starting materials for medicinal products should have an appropriate quality system to document the process used and provide a record for each batch of starting material collected. They should either have, or work towards, official accreditation of the quality system. Procedures should also be in place to reduce the risks of adulteration of batches.

The sources and types of starting materials, while important, are not necessarily the only determinant of risk of potential TSE transmission. Some manufacturing processes—for example those used to produce serum albumin and tallow derivatives—have substantial ability to eliminate infectivity that might be present in the starting material. Processes that inactivate infectivity or remove infectivity from starting materials augment the safety provided by sourcing. Manufacturers should consider including such procedures in their manufacturing processes for starting materials. Claims that a production process contributes significantly to the safety of a product should be validated.

3.2.3 Production systems

Vaccines

The consistent production of safe and effective vaccines poses special problems, because many of them are prepared from organisms that cannot be treated with harsh methods of extraction or purification without reducing or destroying their antigenicity. Additional difficulties are inherent in the cell bank and seed lot systems employed to produce many vaccines.

Production systems impact the TSE risk assessment. Concerns with respect to TSE may arise from an animal used for *in vivo* production or as a source of cells for production *in vitro*, from components of any medium used in production, or from the cell banks or seeds used to initiate production. Where vaccines are grown in animals, careful selection of source materials and, in some cases, postmortem testing of each production animal can greatly reduce the TSE risk. Some vaccines are produced in primary cell cultures, usually derived from animals not known to have TSEs; such cultures are very unlikely to be infected or contaminated with TSE agents. However,

any culture medium used in the growth of bacterial, yeast, mammalian or other cells *in vitro* may contain components of animal origin. Such media should be evaluated for TSE risk.

The most complex TSE issues are raised by banked eukaryotic or bacterial cells and viral vaccine seeds. The group strongly emphasized that, by virtue of the level of characterization possible, the overall risk-benefit assessment overwhelmingly favors the use of banked cells and the seed lot system for viral vaccine production. However the TSE risk assessments of banked cells and viral vaccine seed stocks should take into account the possible carryover of any potentially infectious material from the seed into the final product as a contaminant. There is also a theoretical possibility that production cells might be infected with a TSE agent, although none of the very few cell lines that are known to support replication of a TSE agent has been used to produce any vaccine.

When evaluating the possibility of potentially infectious material in a seed, not all relevant information may be available; since seeds often have a lifetime of decades, tracing their origin and full production history may be impossible. Where information is incomplete, it is recommended that working seeds be replaced as a precautionary measure, taking into account the need to maintain adequate supplies of vaccines with public health benefits during the replacement. For existing products, master seed materials and original experimental preparations from which master seeds are derived (“pre-master” seeds) may not need replacement, since the biological phenotype of the vaccine depends on these materials, and they may be difficult or impossible to recreate. However, the goal of eventually replacing all seeds with those of impeccable provenance for all reagents should not be abandoned. The origin of newly developed products should be documented as completely as possible, recognizing that this may also be difficult. For new products made using old seed lots, any existing risk assessment for the seed and history of prior use of the seed should be taken into account.

Initiation of production of seed materials for new vaccines (either new cell banks or viral or bacterial seeds) should also take into account all guidance on TSE risk in force at the time that laboratory work begins. However, it is recognized that research and development for new vaccines often takes years; complete information on TSE risk for older seed materials may not meet requirements in force later, when a candidate new product must be assessed for final licensure. The principles outlined above, in the paragraph on seed materials, should be applied in such cases.

Recombinant DNA products

Medicines produced by recombinant DNA technology use a cell banking system similar to that used for many vaccines. Similar considerations with respect to production media, carryover of contaminants and the theoretical possibility of infection of the cells therefore apply. Risk assessments should be based on the same approaches used for vaccines.

Other medicinal products

A number of bovine derived materials are commonly used to manufacture both biological and pharmaceutical products. These include milk and milk derivatives, meat extracts, bovine serum including fetal bovine serum, bovine bone gelatin and beef tallow derivatives. Materials originating from other ruminant species are less commonly used.

Milk and certain milk derivatives, such as lactose, are generally considered non-infectious, regardless of geographic origin, provided that the milk is from healthy cows fit for human consumption and no other potentially infectious ruminant-derived materials were used in the manufacturing process.

Extracts prepared from tissues like bovine muscle, in which TSE infectivity has not been detected, are unlikely to present any risk of TSE contamination, provided that the manufacturer has scrupulously complied with procedures designed to avoid cross contamination during preparation of the source material; if assurances of compliance are not available, then it is recommended to collect meat extracts from animals in countries where risk of BSE is remote.

TSE infectivity has been detected in transfused blood of sheep with natural scrapie and with experimental BSE infections. Similar experiments have not been conducted in bovines nor has the effect of blood clot formation on TSE infectivity in serum been established. Studies using smaller amounts of blood components and spleen of cattle with BSE assayed in mice and cattle have failed to detect infectivity. A conservative regulatory approach would assume that bovine serum might potentially contain TSE infectivity—presumably in small amounts. Blood for the preparation of donor calf serum is most often collected from well controlled living animals, reducing the risk of cross contamination of blood with higher risk materials attendant to the stunning and slaughtering process. Thus the sourcing of bovine serum (country/herd/animal) combined with appropriate precautions to avoid cross contamination during collection is important in the risk analysis.

Gelatin may be extracted from the skin and/or bones of cattle. Gelatin extracted from skins has a lower risk than does gelatin extracted from bones—especially bones from which skulls and vertebral columns have not been carefully excluded—because hide gelatin offers little opportunity for cross contamination with potentially infective tissue (for example brain, spinal cord and ganglia). Thus, it is recommended to collect bovine bones for processing into gelatin only from BSE-free countries or from countries with a low prevalence of BSE; it is preferable to exclude skull and vertebral columns from bones used for gelatin. The use of bone gelatin produced by alkaline hydrolysis (augmented, whenever possible, by additional approved processes) rather than by acid treatment alone further reduces the risk of contamination with TSE agents. Compliance with these precautions provides assurance that gelatin used in the manufacture of medicinal products is unlikely to be contaminated. Amino acids derived from gelatin are further highly processed, so their risk may be even lower.

Materials derived from ruminant tallow (for example, triglycerides, glycerol, sorbitan esters, polysorbate etc.) or amino acids of ruminant origin (even if higher-risk tissues were not completely eliminated) are considered highly unlikely to remain contaminated by the time the final reagent has been produced, so long as they were prepared by processes of extraction and purification at high temperatures and if good manufacturing practices (GMP) were rigorously controlled.

3.3 Measures to minimize risks to humans from human-derived materials

3.3.1 The risk of transmission of CJD and vCJD by blood and blood products

For many years it has been known that infectivity can be detected in the blood of rodents experimentally infected with certain TSE agents, including BSE agent. In the rodent models, infectivity is detected in both plasma and cellular components. Infectivity has also been detected in

buffy coat of primates experimentally infected with BSE and in whole blood and buffy coat of sheep with experimental BSE. Most recently, infectivity has been detected in blood of sheep with scrapie—the first evidence of infectivity in blood in a naturally occurring TSE.

No credible instance of transmission of CJD by human blood, blood components or plasma derivatives has been reported, and an increasing number of epidemiological investigations over many years have failed to find any evidence that a history of treatment with blood components or plasma products is associated with increased risk of CJD. Among hemophiliacs treated with clotting factor concentrates derived from plasma there have been no reports of CJD to date, and postmortem examination of brain tissue from patients with hemophilia have not detected evidence of CJD. No transmission of vCJD by blood, blood components or plasma derivatives has been observed, despite the fact that, in the UK, several patients received blood from donors who later developed vCJD. Experience with vCJD—first recognized less than ten years ago—is limited, and epidemiological surveillance of surviving recipients of those blood products is underway. Attempts to transmit disease to monkeys and mice from blood of patients with vCJD have also been negative to date¹.

In spite of these reassuring results, the documented occurrence of infectivity in one natural and several experimental TSEs of animals continues to generate concern about risk from the blood of humans with TSE. Unfortunately, there is still no diagnostic test available that can be used to screen donors at risk of transmitting CJD or vCJD. In the absence of such tests, precautionary exclusion of donors at increased risk of CJD remains the only available measure to reduce the theoretical risk of transmitting CJD by blood products, and a number of countries have instituted such a measure.

Experimental studies from several research groups has consistently shown substantial reduction of spiked TSE infectivity during plasma fractionation steps, and there is growing evidence that the risk from plasma derivatives is negligible. It has also been shown that nanofiltration can reduce or eliminate TSE infectivity spiked into blood, but the method has so far been applied only to a limited number of plasma products. Precautionary leucodepletion of blood components has been introduced in a number of countries to reduce non-haemolytic febrile reactions and infections with some cell-associated viruses, but it has not been shown to reduce TSE infectivity.

Human albumin is used as a growth medium or stabilizer in a number of biological products, including vaccines. Some countries have implemented a policy to withdraw products containing plasma-derived medicinal products, including products containing albumin as an excipient, when post-donation information reveals that a donor who contributed to the plasma pool has developed vCJD. Withdrawal of batches of medicinal products containing albumin as an excipient might cause shortages of needed products, such as vaccines. To avoid such a situation, the group encouraged developing alternatives to plasma-derived albumin for excipient use.

3.3.2 Donor deferral policies

Classical CJD and other human TSEs except vCJD

The current internationally recognized donor selection criteria should be maintained. This implies that the following donors should be excluded because of increased CJD risk:

¹ Unpublished information provided by Dr P. Brown

-
- Donors who have been treated with extracts derived from human pituitary glands (growth hormone, gonadotropin)
 - Donors who have a family history of CJD or a similar TSE
 - Donors who have received a human dura mater graft

National regulatory authorities generally recommend discarding blood components (red cell concentrates, platelets and plasma) still in inventory when post-donation information reveals that a donor has CJD or a risk factor for CJD.

Although there is a significant probability that any large plasma pool contains a donation from a person who will eventually develop CJD (the estimated lifetime risk of CJD in the general population being approximately one per ten thousand), epidemiological studies have consistently failed to find any evidence that plasma derivatives have transmitted CJD. As noted, some plasma fractionation steps were effective in clearing substantial amounts of spiked infectivity, reducing the risk of transmission. Furthermore, when precautionary withdrawals of plasma derivatives were attempted after post-donation reports of CJD or CJD risk factors in a donor, those withdrawals contributed to severe shortages of certain derivatives. Considering the reassuring epidemiological data and the overall adverse effect that shortages would cause, there has been general agreement that products prepared from large pools of plasma need not be withdrawn from the market when post-donation information reveals that a donor has CJD or a risk factor for CJD.

vCJD

The primary risk for acquiring vCJD appears to be the presence of BSE agent in beef products entering the human food chain. Potential human exposure depends on both “internal” and “external” factors. Internal factors are the geographical risk—the probability that BSE infectivity occurs in cattle of a region and domestic human consumption patterns of bovine-derived products in that region. External factors relate to human exposure to the BSE agent through importation of infected animals or animal products or through exposure while travelling in areas where cattle have BSE or where the agent enters the food supply through imports. The introduction of precautionary measures should take these factors into account.

Because experience with vCJD is comparatively recent, conclusions about the absence of vCJD infectivity in the blood are less secure than for sporadic disease. The possibility that blood of a person incubating vCJD might transmit the infection has led to policies aimed to minimize the risk, and many countries have instituted precautionary deferral of donors who travelled or lived in countries with a potential risk for BSE and vCJD. The periods of time that a suitable donor may have spent in various BSE countries were adjusted for the probable intensity of exposure to the BSE agent in comparison with the UK. After a country has implemented effective food chain controls and other protective measures, the risk of human exposure should be markedly reduced, and time spent there by donors after that is of little concern. Policies on donor suitability should also take into account the estimated effect that various deferral criteria might have on the blood supply. It may be reassuring to note that for those countries unlikely to have BSE in cattle or the BSE agent in food and from which few citizens have travelled to countries with BSE there is a negligible risk of blood-borne vCJD.

Despite reassuring evidence that plasma fractionation reduces the risk of transmission by plasma derivatives, as a prudent measure until more experience is gained with this new disease,

it is advocated to recall batches of plasma-derived products if a donor with vCJD is recognized after donation. Withdrawal of plasma derivatives is not recommended when a donor is recognized post-donation to have any form of CJD other than vCJD or to have had a risk factor for any form of CJD, or when post-donation information reveals that a donor was unsuitable due to travel or residence in BSE countries.

3.3.3 Human cells, tissues and tissue derived products

In addition to theoretical transmission of TSE through blood products, transmission by human tissues is possible, either because of inherent cellular infectivity or contamination by residual blood or plasma. In principle, although the same precautions should be applied to the transfer of cells and tissues as to blood, the risk-benefit assessment of TSE transmission versus therapeutic need should determine the use of such products. For example, the need for a rare type of bone marrow matched only from a UK resident would outweigh the remote possibility of TSE transmission. That policy might not be appropriate for another human tissue, like cornea, that is more readily available and that need not be carefully matched. Thus, the risk-benefit estimate for therapeutic administration of cells and tissues is probably best decided on a case-by-case basis.

4. CONCLUSIONS

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 potential benefits to patients. Recommendations are intended to apply to all medicinal products for which active substances, excipients or reagents derived from bovine tissues are used during their production processes. The recommendations relate particularly to materials of bovine origin, but 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. The development of substitutes for bovine, ovine or caprine materials used to manufacture medicinal products is encouraged. However it is recognized that this may not always be feasible, given the current level of scientific development for some products. This goal is sufficiently important to justify taking a long-term approach to reach it.

It is emphasized that, when considering precautionary measures to maintain the safety of blood products, authorities should take into account their possible effect on the supply of blood. In that regard, it seems premature to recommend a global uniform policy, and every country should decide if precautionary measures are indicated to reduce the theoretical risk of transmitting CJD and vCJD by blood products.

Participants felt it important to stress that eliminating inappropriate use of blood and blood products would substantially reduce the risk of transfusion-related adverse events including the theoretical risk of blood-borne transmission of TSEs. Development of reliable methods to remove or inactivate the agents of TSE agents during the processing of blood and plasma remain of paramount importance and are to be encouraged, as are efforts to develop and validate sensitive and specific antemortem TSE diagnostic tests suitable for donor screening and tests for qualifying donor units as free of TSE agents.

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MAJOR CATEGORIES OF INFECTIVITY : TABLE IA, IB, IC

The information in the Tables is based exclusively upon observations of naturally occurring disease, or primary experimental infection by the oral route (in cattle), and does not include data on models using strains of TSE that have been adapted to experimental animals, because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease. Because immunohistochemical and/or western blot detection of misfolded host protein (PrP^{TSE}) have proven to be a reliable indicator of infectivity, PrP^{TSE} testing results have been presented in parallel with bioassay data. Tissues are grouped into three major infectivity categories, irrespective of the stage of disease:

- IA: High-infectivity tissues: CNS tissues that attain a high titre of infectivity in the later stages of all TSEs, and certain tissues that are anatomically associated with the CNS.
- IB: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE.
- IC: Tissues with no detectable infectivity: tissues that have been examined for infectivity and/or PrP^{TSE} with negative results.

Although the category of lower risk tissues almost certainly includes some (e.g., blood) with a lower risk than others (e.g., lymphoreticular tissues), there are so few data about infectivity levels in these tissues that no attempt was made to subdivide the category into different levels of risk. It is also evident that the placement of a given tissue in one or another category can be disease specific, and subject to revision as new data accumulate.

Data entries are shown as follows:

- + Presence of infectivity or PrP^{TSE}
- Absence of detectable infectivity or PrP^{TSE}
- NT Not tested
- NA Not applicable
- ? Controversial or uncertain results
- () Data limited to one or two tested specimens (human tissues)

Table IA: High-infectivity tissues

CNS tissues that attain a high titre of infectivity in the later stages of all TSEs and certain tissues anatomically associated with the CNS								
Tissues	Human TSEs				Cattle		Sheep & goats	
	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity ₁	PrP ^{TSE}	Infectivity ₁	PrP ^{TSE}	Infectivity ₁	PrP ^{TSE}	Infectivity ₁	PrP ^{TSE}
Brain	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+
Retina, Optic nerve	+	+	+	+	+	NT	NT	+
Spinal ganglia	NT	+	NT	+	+	NT	NT	+
Trigeminal ganglia	NT	+	NT	+	+	NT	NT	+
Pituitary gland ²	NT	+	NT	+	-	NT	+	NT
Dura mater ²	NT	-	NT	-	NT	NT	NT	NT

Table IB: Lower-infectivity tissues

Peripheral tissues that have tested positive for infectivity and/or PrP ^{TSE} in at least one form of TSE								
Tissues	Human TSEs				Cattle		Sheep & goats	
	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}
<i>Peripheral Nervous system</i>								
Peripheral nerves	NT	+	(-)	+	-	NT	+	NT
Enteric plexuses ³	NT	?	NT	(-)	NT	+	NT	+
<i>Lymphoreticular tissues</i>								
Spleen	+	+	+	-	-	-	+	+
Lymph nodes	+	+	+	-	-	-	+	+
Tonsil	+	+	NT	-	+	NT	+	+
Nictitating membrane	NA	NA	NA	NA	NT	-	NT	+
Thymus	NT	+	NT	-	-	NT	+	NT
<i>Alimentary tract</i>								
Esophagus	NT	-	NT	-	-	NT	NT	+
Fore-stomach ⁴ (ruminants only)	NA	NA	NA	NA	-	NT	NT	+
Stomach/abomasum ⁴	NT	-	NT	NT	-	NT	NT	+
Duodenum	NT	-	NT	NT	-	NT	NT	+
Jejunum ⁵	NT	+	NT	-	-	NT	NT	+
Ileum ^{5,6}	NT	+	NT	-	+	+	+	+
Large intestine ⁵	NT	+	NT	-	-	NT	+	+
<i>Reproductive tissues</i>								
Placenta ⁷	NT	-	(+) ?	-	-	NT	+	+
<i>Other tissues</i>								
Lung	NT	-	+	-	-	NT	-	NT
Liver	NT	-	+	-	-	NT	+	NT
Kidney	NT	-	+	-	-	-	-	-
Adrenal	NT	+	-	-	NT	NT	+	NT
Pancreas	NT	-	NT	-	-	NT	+	NT
Bone marrow	NT	NT	(-)	-	+	NT	+	NT
Blood vessels	NT	+	NT	+	-	NT	NT	+
Olfactory mucosa	NT	NT	NT	+	-	NT	+	NT
Gingival tissue	NT	NT	-	-	NT	NT	NT	NT
Salivary gland	NT	NT	NT	NT	-	NT	+	NT
Cornea ⁸	-	-	+	-	NT	NT	NT	NT
<i>Body fluids</i>								
CSF	NT	-	+	-	-	NT	+	NT
Blood ⁹	-	-	-	-	-	NT	+	-

Table IC: Tissues with no detected infectivity

Tissues with no detected infectivity								
Tissues	Human TSEs				Cattle		Sheep & goats	
	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}	Infectivity	PrP ^{TSE}
Reproductive tissues								
Testis	NT	-	(-)	-	-	NT	-	NT
Prostate/ Epididymis/ Seminal vesicle	NT	-	(-)	-	-	NT	-	NT
Semen	NT	-	(-)	-	-	NT	NT	NT
Ovary	NT	-	NT	-	-	NT	-	NT
Uterus (Non-gravid)	NT	-	NT	-	-	NT	-	NT
Placenta fluids	NT	NT	(-)	NT	-	NT	NT	NT
Fetus ¹⁰	NT	NT	NT	NT	-	NT	-	NT
Embryos ¹⁰	NT	NT	NT	NT	-	NT	?	NT
Musculo-skeletal tissues								
Bone	NT	NT	NT	NT	-	NT	NT	NT
Skeletal muscle ¹¹	NT	-	-	-	-	NT	-	NT
Tongue	NT	-	NT	-	-	NT	NT	NT
Heart/pericardium	NT	-	-	-	-	NT	-	NT
Tendon	NT	NT	NT	NT	-	NT	NT	NT
Other tissues								
Trachea	NT	-	NT	-	-	NT	NT	NT
Skin	NT	-	NT	-	-	NT	-	NT
Adipose tissue	NT	-	(-)	-	-	NT	NT	NT
Thyroid gland	NT	-	(-)	-	NT	NT	-	NT
Mammary gland/udder	NT	NT	NT	NT	-	NT	-	NT
Body fluids, secretions and excretions								
Milk ¹²	NT	NT	(-)	NT	-	NT	-	NT
Colostrum ¹³	NT	NT	(-) ?	NT	NT	NT	-	NT
Cord blood ¹³	NT	NT	(-) ?	NT	-	NT	NT	NT
Saliva	NT	-	-	NT	NT	NT	-	NT
Sweat	NT	NT	-	NT	NT	NT	NT	NT
Tears	NT	NT	-	NT	NT	NT	NT	NT
Nasal mucus	NT	-	-	NT	NT	NT	NT	NT
Urine ^{13,14}	NT	NT	-	-	-	NT	NT	NT
Feces	NT	NT	-	NT	-	NT	-	NT

Table Footnotes

1. Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats not all results are consistent for both species.
2. No experimental data about infectivity in human pituitary gland or dura mater have been reported, but cadaveric dura mater patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to scores of people and therefore must be included in the category of high-risk tissues.
3. In cattle, limited to the distal ileum.
4. Ruminant forestomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.
5. In vCJD, positivity is limited to gut-associated lymphoid tissue (mucosa, muscle, and serosa are negative).
6. In cattle and sheep, only the distal ileum has been bioassayed for infectivity.
7. A single report of transmission of CJD infectivity from human placenta has never been confirmed and is considered improbable.
8. Because only one or two cases of CJD have been plausibly attributed to corneal transplants among hundreds of thousands of recipients, cornea is categorised as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.
9. Early reports on the transmission of disease to rodents from the blood of patients with sCJD have not been confirmed, and evaluation of the ensemble of experimental and epidemiological data relevant to TSE transmission through blood, blood components, and therapeutic plasma products fails to suggest transmission from blood of patients with any form of 'classical' TSE. Not enough data has accumulated to be able to make the same statement about blood from patients with vCJD. Fetal calf blood contains no detectable infectivity, but in genotypically susceptible sheep with natural scrapie or experimentally induced BSE, transfusion of large blood volumes has transmitted disease to healthy sheep. Infectivity has also been demonstrated in studies of rodent-adapted strains of TSE.
10. Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made on fetal calf tissues other than blood (negative mouse bioassay). Calves born of dams that received embryos from BSE-affected cattle have survived for observations periods of up to seven years, and examination of the brains of both the unaffected dams and their calves revealed no spongiform encephalopathy or PrP^{TSE}.
11. Intracerebral inoculation of muscle homogenates has not transmitted disease to 1) primates from humans with sCJD; 2) mice or cattle from cattle with BSE; and 3) mice from sheep and goats with natural or experimentally-induced scrapie. However, older reports described single instances of transmission from goat and hamster muscle, and a more recent report described transmission from the muscle of wild type and transgenic mice, but as each of these studies were conducted with passaged strains of TSE, their relevance to natural disease remains undetermined. A recent human case report described a patient with CJD and inclusion body myositis with abundant PrP^{TSE} in diseased muscle. After much deliberation, the committee nevertheless elected to retain muscle in the 'no detected infectivity' tissue category until more information about uncomplicated natural infections becomes available.
12. Evidence that infectivity is not present in milk includes temporo-spatial epidemiologic observations failing to detect maternal transmission; clinical observations of over a hundred calves nursed by infected cows that have not developed BSE; and experimental observations that milk from infected cows has not transmitted disease when administered intracerebrally or orally to mice. Experiments are in progress in which large volumes of milk from experimentally infected cows are concentrated and tested for the presence of PrP^{TSE}.
13. Single reports of transmission of CJD infectivity from human cord blood, colostrum, and urine have never been confirmed and are considered improbable.
14. A previously unreported PrP type, termed PrP^u, has been identified in the urine of sporadic and familial CJD patients, but its significance for transmission risk remains to be determined.

TABLE REFERENCES

The Tables IA, IB and IC were created by an *ad hoc* expert group formed during the Consultation, the members of which were Mr R. Bradley; Dr P. Brown; Prof. Dr H. Budka; Prof. Dr D. Dormont; Dr M. Groschup; Dr B.E.C. Schreuder; Mr G.A.H. Wells. Dr P. Brown coordinated the *ad hoc* expert group and consolidated the data and information provided after the Consultation.

Most of the observations that form the basis for the Table have been published in original reports (or cited in reviews) that follow. No attempt has been made to list the many reports in which only one or two tissues were examined, unless they concerned tissues of exceptional current interest. Also, a number of observations made by, or known to, members of the expert subcommittee that assembled the table, have not yet been published.

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**WHO CONSULTATION ON
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IN RELATION TO BIOLOGICAL AND PHARMACEUTICAL PRODUCTS**

**WHO Headquarters: Geneva
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