European Medicines Agency

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CPMP POSITION STATEMENT ON CREUTZFELDT-JAKOB DISEASE and PLASMA-DERIVED AND URINE-DERIVED MEDICINAL PRODUCTS

This Position Statement replaced the CPMP Position Statement on "New variant CJD and plasma-derived medicinal products" issued in February 1998. It is superseded by EMEA/H/CPMP/BWP/2879/02/rev.1, published in June 2004.

SUMMARY

Cumulative epidemiological evidence and other considerations do not support transmission of sporadic, familial and iatrogenic Creutzfeldt-Jakob disease (CJD) by plasma-derived medicinal products. There is no change to the previous CPMP position that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, familial or iatrogenic CJD.

Variant CJD (vCJD) is an emerging disease, the eventual number of cases of the disease is uncertain, there is a wider distribution and higher level of infectivity/abnormal prion protein in peripheral tissues than is seen with sporadic CJD, and it is not known whether or not infectivity is present in human blood. Therefore, the precautionary approach established in the 1998 Position Statement will be continued.

Available data indicate that the manufacturing processes for plasma-derived medicinal products would reduce infectivity if it were present in human plasma. It is recommended that manufacturers utilise this general information to analyse the potential of their specific manufacturing processes to reduce infectivity. It is also highly desirable that manufacturers undertake product-specific investigational studies on key steps for plasma-derived medicinal products, as a precautionary measure.
In support of this recommendation, CPMP's Biotechnology Working Party, with the involvement of external experts, will develop a "Points to Consider" document to provide guidance on how to investigate manufacturing processes with regard to CJD risk.

Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding to no longer fractionate from UK plasma. It is consistent with this decision to exclude donors who have spent long periods in the UK during the risk period from donating blood/plasma for fractionation. It is recommended that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation.
There is no recommendation to recall batches if information becomes available post-donation, which would have excluded a donor based on his/her stay in the UK since this is a very conservative precautionary measure.

A recent publication has reported the detection of an abnormal prion protein in the urine of animals and humans suffering from transmissible spongiform encephalopathies (TSEs). There is no recommendation for donor exclusions at the present time based on a number of considerations. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK. While information is awaited on whether these results can be confirmed, further consideration will be given to the potential of manufacturing processes for urine-derived medicinal products to reduce infectivity, if it were present in urine.

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1. Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease affecting approximately 1.5 to 2 persons per million population per year. Cases can arise spontaneously (sporadic), may arise at higher frequency in families with certain genetic mutations (familial) or can result from medical exposure to infectious material (iatrogenic). In 1996, a variant form of CJD (vCJD) was identified. There is strong evidence that vCJD is caused by the agent responsible for bovine spongiform encephalopathy (BSE) in cattle. The most likely hypothesis is that vCJD has occurred through exposure to BSE contaminated food.

Human transmissible spongiform encephalopathies (TSEs), including in particular vCJD, were addressed in expert meetings/workshops at the EMEA in January 1998, January 1999, December 1999, May 2000, and December 2000. A CPMP Position Statement on variant CJD and plasma-derived medicinal products was issued in February 1998[1d] and the outcome of the subsequent meetings was published on the EMEA website[1].
An EMEA Expert Workshop on Human TSEs and Medicinal Products was held on 19-21 June 2002. The aims of the workshop were:

- To review the latest information on human TSEs
- To reconsider the precautionary measures already in place
- To consider further precautionary measures that might be introduced
- To consider whether precautionary measures could be harmonised in all Member States
- To provide the scientific basis for the preparation of this CPMP Position Statement.

A report of the June 2002 meeting will be published on the EMEA website.

This document replaces the previous CPMP Position Statement.

Blood and blood components for transfusion are outside the scope of this Position Statement. Recommendations on the suitability of blood and plasma donors and the screening of donated blood in the European Community are described in Council Recommendation 98/463/EC[2]. The Scientific Steering Committee (SSC) and the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) of the European Commission have published a number of opinions relating to TSEs, which are of relevance to blood and blood components for transfusion, as well as to plasma-derived medicinal products[3]. The Council of Europe has also made recommendations for blood and blood components for transfusion[4].

2. Variant CJD current status

The official UK figures for vCJD at the beginning of February 2003 were a total of 130 definite or probable vCJD cases. (One case in Hong Kong was a UK case and is included in the UK figures.) Outside of the UK, there has been one case in Ireland, one in the USA, and one in Canada, who were probably infected while in the UK. However, none of the 6 cases in France and 1 case in Italy had spent time in the UK. The possibility of cases occurring in other countries cannot be excluded.
All cases, who have been genotyped so far, are homozygotes (Met-Met) at codon 129 of the prion protein (PrP) gene.

3. Human tissue distribution of infectivity/abnormal prion protein.

Tissue distribution has been investigated by detection of the abnormal prion protein (PrP^{sc}/PrP^{res})[a] or by infectivity assays. Until now, detection of PrP^{sc} in tissues has always been associated with infectivity, however it should be noted that animal studies show that, in some circumstances,

[a] PrP^{sc} is an abnormal isoform of the natural protein PrP^{c}, which is anchored to the surface of many cells in mammals. PrP^{c} and PrP^{sc} have a different resistance towards proteinase K treatment: the endogenous PrP^{c} is completely degraded by proteinase K, whereas PrP^{sc} is partly resistant (giving rise to PrP^{res}).

infectivity can also be present without detection of PrP^{sc}. It is thus necessary that any study on tissue or fluid distribution of the prion protein be confirmed with an infectivity assay.
A wider distribution and higher level of PrP^{sc} in human peripheral tissues, including the lymphoreticular system, has been found in vCJD compared with sporadic CJD. Limited data from infectivity assays of tissues are consistent with the PrP^{sc} findings.

4. Infectivity in blood and transmissibility via blood

4.1 Animal blood

Low levels of infectivity have been found in the blood of rodents experimentally infected with TSE agents. This infectivity can be transmitted by intravenous inoculation. Intravenous inoculation is less efficient than intracerebral inoculation. Experimental studies indicate that the vCJD agent behaves in a similar way (qualitatively and quantitatively) to a familial CJD agent[b] when adapted to RIII/Fa/Dk mice.
Information from an on-going intra-species transfusion experiment indicates that experimental BSE in orally infected sheep or natural scrapie infection in sheep can be transmitted to genetically susceptible sheep by blood transfusion. The level of infectivity in blood cannot be established from these experiments.
Infectivity has also been detected in blood of a BSE adapted strain in a non-human primate model.

4.2 Human blood

Infectivity was not detected in blood from patients with sporadic CJD using human PrP - transgenic mice for the detection of infectivity.
Infectivity or PrP^{sc} were not detected in blood of vCJD cases using methods capable of detecting infectivity/PrP^{sc} in peripheral tissues such as tonsil or spleen.
Experiments to detect vCJD infectivity in human blood using transgenic mice and primates for the detection of infectivity are on-going.
The tracing of recipients of blood transfusion from UK donors who have subsequently developed vCJD has not revealed any secondary transmissions. However, there is only a small number of subjects and a short follow-up period at this time.

5. Detection techniques

Several techniques are under development for the detection of PrP^{sc} in blood. Approaches based on surrogate markers are also under investigation. Development and validation of all methods is on-going but there is no screening test yet.
The WHO initiative to make available reference preparations is progressing. These reference preparations will allow calibration of assays versus infectivity bioassays and can be used for collaborative studies to compare the performance of different assays.

6. Leucoreduction

Leucoreduction is used in transfusion medicine to reduce the level of white blood cells in blood and blood components.
The rationale for considering leucoreduction as a precautionary measure is:
- The lymphoreticular involvement in vCJD
- The detection of low levels of infectivity, in studies with rodents, in the buffy coat (associated with white blood cells)

[b] Mouse-adapted Fukuoka-1 strain of human TSE (brain tissue obtained from a case of Gerstmann-Sträussler-Scheinker syndrome).

The SCMPMD opinion on leucoreduction[3a, 3b] for blood and blood components for transfusion states that it might be a precautionary step to remove white blood cells as completely as possible. For plasma for fractionation the opinion states the following:
"Taken together, there is no compelling scientific evidence to date for the introduction of leucoreduction of plasma for fractionation, or other methods aiming at removal of cells and debris, as a precaution against vCJD transmission. The question should be further explored by suitable experiments."
For plasma-derived medicinal products, there is a theoretical concern that leucoreduction of blood might encourage dissociation of infectivity from white blood cells resulting in an increase in infectivity in the plasma compartment.
Reassuringly, UK studies on leucoreduction show that it does not provoke fragmentation of cells and lysis.

There is no data to support the effectiveness of leucoreduction at the present time. There is a need for studies investigating leucoreduction of infected blood using infectivity assays.

7. Manufacturing processes for plasma-derived medicinal products

Many investigational studies have now been carried out with different strains of agent and spiking materials of different nature and purity, and using different assays to follow the partition of PrP^{res} and/or infectivity. *In vitro* assays can be useful for spiking experiments to investigate manufacturing processes but it is important to correlate such results with those from infectivity assays, as has already been reported in publications in this area.

These studies have investigated the contribution of the various manufacturing steps to reduction of infectivity (including precipitation, centrifugation, depth filtration, chromatography and nanofiltration). Data support the removal of infectivity by steps that are commonly used in the manufacture of plasma-derived medicinal products. However, caution is needed in the interpretation of data since the effectiveness of a given step is dependent on a number of variables (including the process conditions and state of the agent in the sample). Consequently, effectiveness of removal may vary from one manufacturer to another.

Animal studies using blood from rodents infected by intracerebral inoculation indicate that the fractionation process contributes to the removal of infectivity. However, caution is needed in the interpretation of spiking studies since there are indications from preliminary information that endogenous infectivity might persist further through the fractionation process than would be expected from spiking studies.

8. Infectivity in urine

The question of whether infectivity is present in urine has not been extensively studied. Shaked et al.[5] reported the detection of a protease resistant PrP isoform ($UPrP^{sc}$) in the urine of hamsters, cattle and humans suffering from TSEs. However, it is noteworthy that intracerebral inoculation of hamsters with $UPrP^{sc}$ did not cause clinical signs of prion disease. These findings need to be repeated and confirmed by other groups.
Epidemiological evidence in the last 25 years, when urinary-derived medicinal products and particularly gonadotrophins have been widely used, does not suggest a risk from sporadic CJD. Since epidemiological evidence has identified the few cases of iatrogenic transmission of CJD through the use of pituitary-derived gonadotrophins, it could be expected that transmission from urinary-derived gonadotrophins would have been detected if it had occurred.

The finding of $UPrP^{sc}$ could open an alternative approach to the development of a test for CJD.

9. Recommendations and proposals

9.1 Sporadic, familial and iatrogenic CJD and plasma-derived medicinal products

Cumulative epidemiological evidence and other considerations do not support transmission of sporadic, familial and iatrogenic CJD by blood, blood components or plasma-derived medicinal products. Nevertheless, donor selection criteria include criteria to exclude donors who might be at higher risk of developing CJD.
On the basis of the current evidence, the CPMP recommendation that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having CJD is still valid.

9.2 Variant CJD and plasma-derived medicinal products

Variant CJD is a new emerging agent. Uncertainties still exist concerning the number of cases of vCJD that will occur and whether or not infectivity is present in blood. Variant CJD has a different peripheral distribution to sporadic CJD. Epidemiological experience is too limited to reach conclusions on whether or not vCJD could be transmitted by blood, blood components or plasma-derived medicinal products.
For these reasons, it is prudent to maintain a precautionary approach and recommend measures aimed at minimising the risk of transmission of the agent, if it were present in human blood and plasma.

9.2.1 Exclusion Criteria

a) Consideration of Country-based exclusions

Variant CJD sufferers with overt disease will be too ill to present for donation or would be disqualified at the point of donor screening. However, there is no screening test to detect donors who may be incubating the disease or in the early clinical stages. Therefore, other approaches are considered in order to try and identify donors who may present a higher risk.

UK plasma
Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to fractionate from UK plasma.

Exclusion of donors based on cumulative period of time spent in the UK
Since UK donors are excluded from donating plasma for the manufacture of plasma-derived medicinal products in the UK, it is consistent to exclude donors who have spent long periods in the UK. This is supported by the finding of vCJD cases, which have a risk factor of long periods spent in the UK, in other countries[c].

The benefit of excluding donors who have spent long periods in the UK has to be balanced against the risk of shortages of blood and plasma for the manufacture of medicinal products and for transfusion[d]. The benefit/risk balance differs within Europe compared with the USA because the pattern of travelling to the UK is different. More people within the EEA travel to the UK and there is more travelling for shorter periods of time. This is illustrated by a comparison of the analysis made by the USA and France[6c]. The analysis considered that a one-day stay in the UK corresponds to an arbitrary unit risk of one person-day, and that the risk is cumulative (e.g. a 10-day stay represents a risk of 10 person days, and a 30-day stay by one person represents an equivalent cumulative risk to 30 one-day stays by different individuals).

[c] One case in each of Ireland, US and Canada associated with long periods spent in the UK.
[d] It is emphasised that there needs to be separate considerations for blood and blood components for transfusion as these products are mainly used within national boundaries. This is outside of the scope of this Position Statement.

	FRANCE		USA	
Cumulative stay in UK	**% of donors concerned**	**% of exposure linked to stays in UK**	**% of donors concerned**	**% of exposure linked to stays in UK**
≥ 6 months between start of 1980 and end of 1996	1.29%	63%	2.2%	87%

It was concluded from the French analysis that to achieve a 90% reduction in the cumulative exposure to the risk of BSE linked to stays in the UK it would be necessary to exclude all donors who have spent more than 15 days in the UK (approximately 11% of donors). In contrast, a similar reduction in the cumulative exposure could be achieved in the USA by excluding only about 2% of donors.

In addition to differences between Europe and the USA, there are differences between European countries in their travel patterns to the UK. An exclusion of donors who have spent a cumulative period of 6 months or more in the UK would exclude approximately 13% of Irish donors and 5% of Norwegian donors compared with the 1.29% in France.

Furthermore, residence in the UK is not the only risk factor and cases have occurred in France and Italy without an association with UK residence.
The most likely hypothesis is that vCJD has occurred through exposure to BSE contaminated food. Therefore, in addition to risk associated with time spent in the UK, there is the endogenous risk within a country via the food chain related to the BSE incidence within the country and the level of BSE infected/contaminated imports. European countries have different degrees of endogenous risk. The UK risk is substantially higher than that of any other country. France has estimated that the endogenous risk was 1/20 of that in the UK whereas Finland detected its first BSE case in 2001 and had no import of meat from the UK during the risk period.

The above considerations have led to different decisions within the EEA on exclusion of donors who have spent time in the UK (no exclusion, 5 years, 1 year or 6 months). These different decisions have the potential to create difficulties with the movement of plasma-derived medicinal products between Member States. To avoid such problems, it is desirable to have agreement on the exclusion measure that will be accepted.
It is, therefore, recommended that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation. Countries are highly encouraged to choose their national cumulative period limit for plasma-derived medicinal products according to a nationally calculated benefit/risk balance, which will take into account the endogenous risk of BSE and the risk of shortages of blood and plasma for the manufacture of medicinal products. The national limit is recommended to be of cumulative periods in the UK below or equal to 1 year, since for plasma-derived medicinal products, there is very little difference in effectiveness of the measure between an exclusion of 3 months, 6 months or 1 year in the UK.
Countries may still apply a stricter limit than 1 year for exclusion of donors for blood/plasma collected for fractionation within the country (e.g. 6 months) but will accept plasma-derived medicinal products from other countries provided that at least the one-year time limit is applied.

The rationale for this recommendation is to exclude donors who have the highest individual risk from stays in the UK and to be consistent with the UK decision to no longer fractionate from UK plasma. The above mentioned French analysis indicates that there is little difference between a time period of 6 months or 1 year in terms of reduction in cumulative exposure to the risk of BSE, linked to stays in the UK. This is illustrated in the following table.

Information taken from French analysis of cumulative exposure to the risk of BSE linked to stays in the UK[6c]

Cumulative stay in UK (between start 1980 and end 1996)	**% of donors concerned**	**% of exposure linked to stays in UK**
≥ 3 months	2.28%	70.82%
≥ 6 months	1.29%	63.04%
≥ 1 year	0.71%	54.33%
≥ 5 years	0.12%	22.04%

Member States who do not currently apply an exclusion of donors based on time spent in the UK will require time for implementation of this measure. The safety of batches of product manufactured from blood/plasma collected before the implementation of the measure is not in question. Therefore, such batches can stay on the market and are not subject to any batch recall.

French plasma

France is currently the only country outside the UK that has had a number of vCJD cases, which are not linked to stays in the UK. France has estimated a risk of 1/20 of that in the UK. France published an analysis of the risk of transmission of vCJD by blood and its derivatives sourced from French plasma in December 2000[6b]. This concluded that plasma collected in France could continue to be used for fractionation. The safety margin for plasma-derived medicinal products was considered to be sufficient. However, a further increase in the safety margin of some products was recommended (e.g. nanofiltration of Factor VIII introduced in January 2001). Leucodepletion for plasma for fractionation, as for plasma for transfusion, was also recommended as a precautionary measure. A subsequent analysis published in February 2002 re-confirmed these conclusions[6a].

Donors who have spent a cumulative period of time in France

Exclusion of donors who have spent a cumulative period of time in France is not recommended because of the lower risk associated with time spent in France compared with time spent in the UK. On the basis that the risk in France is 1/20 of that in the UK, a donor spending a cumulative period of one year in the UK would be equivalent to a donor spending 20 years in France during the risk period.

Concluding remarks

Country-based exclusions are inefficient, as the vast majority of donors who will be excluded will not develop the disease. There is a lack of spare plasma capacity to make up for shortfalls if countries that are major producers of plasma-derived medicinal products discontinue the use of nationally collected plasma for fractionation.

b) Other possible exclusion criteria

Other possible exclusion criteria that could be considered include permanent exclusion of recipients of blood transfusion (general exclusion or transfusion in UK[e]), transplant recipients, and donors who have undergone neurosurgery.

Caution is needed because of the risk of loss of donors and consequent supply problems. Since such criteria could apply to both blood and blood components, and plasma-derived medicinal products, it may be appropriate to consider this further within the scope of the Blood Directive[f] that has recently come into force.

[e] The numbers of donors outside the UK who have spent a cumulative period of less than one year in the UK but have received a blood transfusion within the UK is expected to be very small and it may not be worthwhile to have a specific measure.

[f] Directive 2002/98/EC of the European Parliament and Council setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83 EC, OJ L 33, 8.2.2003, pp 30-40

9.2.2 Leucoreduction

For plasma-derived medicinal products, results would be needed from studies investigating leucoreduction of infected blood using infectivity assays before making any recommendation. (See Section 6 for further discussion of this aspect.)

9.2.3 Manufacturing processes for plasma-derived medicinal products

The available data support the reduction of infectivity by steps in the manufacturing process. It is recommended that manufacturers utilise this general information to analyse the potential of their specific manufacturing processes to reduce infectivity. Where appropriate, manufacturers could consider the addition of steps that may increase the removal capacity, without compromising the safety, quality and availability of the existing products.

Whereas, the general information available on manufacturing processes provides useful background information, the actual effectiveness of a manufacturing process will be dependent on the specific process conditions and, therefore, cannot be extrapolated in a generic way. Given the experience that has now been gathered, and with the knowledge of the time required for these types of studies and their complexity, it is highly desirable that manufacturers undertake product-specific investigational studies on key steps for plasma-derived medicinal products, as a precautionary measure. CPMP will keep progress with this recommendation under review.

In support of this recommendation, CPMP's Biotechnology Working Party, with the involvement of external experts, will develop a "Points to Consider" document to provide guidance on how to investigate, with regard to CJD risk, manufacturing processes (including sanitisation of equipment).

9.2.4 Recall of batches where information becomes available post-donation

In view of the lack of adequate information on vCJD, it is prudent to recall batches of plasma-derived medicinal products where a donor to a plasma pool subsequently develops vCJD. Recall should also include medicinal products containing plasma-derived products as excipients. However, in both cases, consequences for essential medicinal products where alternatives are not available will need careful consideration by the competent authorities.
A case-by-case consideration would be appropriate where plasma-derived products have been used in the manufacture of other medicinal products. This consideration would include the nature of the product, the amount used, where it is used in the manufacturing process and the downstream processing.
Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.
There is no recommendation to recall batches if information becomes available post-donation, which would have excluded a donor based on his/her stay in the UK since this is a very conservative precautionary measure (see 9.2.1).

9.2.5 Albumin used as an excipient or in manufacturing processes

The available data on the removal of infectivity during the fractionation process used in the manufacture of albumin indicates that the risk of transmission of infectivity by albumin would be particularly low. Nevertheless, in the case of albumin used as an excipient, recall is still recommended as a precautionary approach where a donor to a plasma pool subsequently develops vCJD. A single batch of albumin may be used to produce a number of batches of a medicinal product because of the small amounts that are typically used. A recall could affect complete stocks of a product and create severe shortages. Therefore, to avoid a negative impact on supply, companies should consider the origin of plasma and select countries where the probability of having to recall batches is as limited as possible.

Development of substitutes for plasma-derived albumin used as an excipient or in manufacturing processes is encouraged although it is recognised that this can be difficult (requiring development and validation and usually non-clinical and clinical investigations) and should thus be considered as a long-term approach.

9.2.6 Substitution with alternative products

Use of alternative products to plasma-derived medicinal products could be considered, where these are available. It is felt that this choice should remain with users, taking into account the needs of the individual patient. It should be noted that plasma-derived products such as albumin may be used in the manufacture of recombinant products.

9.2.7 Optimal Use

Optimal use of plasma-derived medicinal products is encouraged, as this will maximise the benefits of the products compared with any potential risk.

9.3 Urine-derived medicinal products

Any donor exclusion measure would need to take into account risk factors for sporadic, familial and iatrogenic CJD as well as for vCJD.

On the basis of the following considerations:

- Epidemiological evidence does not suggest a risk for urine-derived medicinal products from sporadic CJD
- The published findings[5] need to be repeated and confirmed
- Intracerebral inoculation of hamsters with $UPrP^{sc}$ did not cause clinical signs of prion disease,

There is no recommendation for donor exclusions at the present time. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK

The situation will be kept under review as information becomes available on whether the published findings can be confirmed. In the meantime, further consideration will be given to the potential of manufacturing processes for urine-derived medicinal products to reduce infectivity, if it were present in urine.

References

1. EMEA published documents

1a) Summary Report of EMEA Expert Meeting on Human TSEs and medicinal products derived from human blood and plasma, 1 December 2000, EMEA/CPMP/BWP/450/01, 28 March 2001. http://www.emea.eu.int/pdfs/human/regaffair/045001en.pdf

1b) Report of EMEA Expert Workshop on Human TSEs and plasma-derived medicinal products, 15-16 May 2000, EMEA/CPMP/BWP/1244/00, 26 July 2000. http://www.emea.eu.int/pdfs/human/regaffair/124400en.pdf

1c) EMEA Workshop on application to pharmaceuticals of assays for markers of TSE, February 1999, CPMP/257/99. http://www.emea.eu.int/pdfs/human/bwp/025799en.pdf

1d) CPMP Position Statement on "New variant CJD and plasma-derived medicinal products", February 1998, CPMP/201/98. http://www.emea.eu.int/pdfs/human/press/pos/020198en.pdf

2. Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community (98/463/EC), OJ L 203 pp.14-26. http://europa.eu.int/eur-lex/pri/en/oj/dat/1998/l_203/l_20319980721en00140026.pdf

3. SSC and SCMPMD published documents

SCMPMD

3a) Opinion on the Safety of Human-Derived Products with Regard to TSE's, adopted on 18 January 2002 http://www.europa.eu.int/comm/food/fs/sc/scmp/out40_en.pdf

3b) Opinion on update of the opinion on the Risk Quantification for CJD Transmission via Substances of Human Origin, adopted on 16 February 2000 http://europa.eu.int/comm/food/fs/sc/scmp/out28_en.pdf

3c) Opinion on the Policy Regarding the Use of Blood and Blood Products adopted by Written Procedure on 24 March 1999 http://europa.eu.int/comm/food/fs/sc/scmp/out20_en.html

3d) Opinion on the risk quantification for CJD transmission via substances of human origin, adopted on 21/10/98 http://europa.eu.int/comm/food/fs/sc/scmp/out12_en.html

SSC

3e) Opinion on the Implications of the Recent Papers on Transmission of BSE by Blood Transfusion in Sheep (Houston et al, 2000; Hunter et al, 2002), adopted September 2002 http://www.europa.eu.int/comm/food/fs/sc/ssc/out280_en.pdf

3f) Opinion on the Implications of the Houston et al paper in The Lancet of 16 September 2000 on the Transmission of BSE by blood transfusion in sheep. (The Lancet, Vol. 356, pp 999-1000; 955-956; 1013) http://europa.eu.int/comm/food/fs/sc/ssc/out143_en.pdf

3g) Oral exposure of Humans to the BSE agent: infective dose and species barrier adopted by the SSC at its meeting of 13-14 April 2000 following a public consultation via Internet between 6 and 27 March 2000
http://europa.eu.int/comm/food/fs/sc/ssc/out79_en.pdf

3h) Opinion on the Human Exposure Risk (HER) via food with respect to BSE - Adopted on 10 December 1999
http://europa.eu.int/comm/food/fs/sc/ssc/out67_en.html

4. Council of Europe Recommendation Rec(2001)4 on the prevention of the possible transmission of variant Creutzfeldt-Jakob Disease (vCJD) by blood transfusion.
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http://www.jbc.org/cgi/reprint/276/34/31479.pdf

6. AFSSaPS published documents

6a) Analyse du risque de transmission de la variante de la maladie de Creutzfeldt-Jakob par les médicaments d'origine humaine et par les produits sanguins labile, actualisation des données du rapport du groupe *ad hoc* de décembre 2000, February 2002
http://afssaps.sante.fr

6b) Analysis of the risk of transmission of new variant Creutzfeldt-Jakob disease by blood and its derivatives", Recommendations of expert group convened at the initiative of AFSSaPS, 11 December 2000.
http://afssaps.sante.fr

6c) Revision of measures to minimise the risk of TSE transmission via blood products", Report of expert group convened under the aegis of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) and the Etablissement Français du Sang (EFS), February 2000.
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