FPS Public Health, Food Chain Safety and Environment
Superior Health Council
Rue de l'Autonomie 4
B-1070 BRUSSELS

Advisory report of the SHC on the actual risk of variant Creutzfeldt-Jakob disease (vCJD) transmission through the transfusion of plasma derivatives of human origin (2005) (SHC 8097)

(Validated by the Transitional Board on 9 November 2005)

I. Request:

On 13 December 2004, the SHC received a request for an advisory report from the Minister's Cabinet (cf. reference a) concerning the actual risk of variant Creutzfeldt-Jakob disease (vCJD) transmission through the transfusion of blood products of human origin, and in particular of stable plasma products.

This request was discussed during the meetings of the working group "Inactivation of prions" that took place on 23 December 2004, 3 February 2005, 2 June 2005, 1 September 2005 and 13 October 2005. Meanwhile, two advisory reports (SCH 8048/2 and 8048/3) were issued on two requests concerning the measures that potentially need to be taken in order to reduce the risk of vCJD-transmission through blood and blood products.

The provisional advisory report of the members of the working group "Inactivation of prions" was approved during the meeting of 13 October 2005 and validated by the SHC Board on 9 November 2005. During the meeting of 8 December 2005, the working group added a reason for the recommendation that was made on traceability.

II. Advisory report:

Executive summary

Assignment

1. Determine the actual risk of vCJD-transmission related to the use of plasma derivatives.
2. Recommend measures concerning the patients that need to be treated.
3. Recommend measures concerning the blood, organ, tissue and cell donor candidates who are believed to have received such products.
4. Assess the consequences of these patients for healthcare professionals, such as doctors, surgeons, dentists and nurses.

Assignment 1

The Superior Health Council (SHC) finds that the actual risk of transmitting the vCJD-agent through the use of plasma derivatives is difficult to assess, the reason being that we know too little about this agent, its physiopathology and the manner in which it is transmitted.
Assessing the efficacy of the separation technologies used for the fractionation of plasma has indicated that most plasma derivatives are subjected to steps that reduce infectivity. A substantial reduction in infectivity was obtained whilst fractionating albumin in experimental simulation.

Given the numerous uncertainties, the SHC takes the view that though very low, the actual risk of transmission may not be excluded, and is impossible to quantify.
The SHC regrets the lack of surveillance and traceability with respect to plasma derivatives in this country and recommends that full traceability from the donor to the recipient, and vice versa, be imposed on all plasma derivatives except those that are used as excipients.

Assignment 2

The SHC emphasizes the importance of carefully selecting the indications for the use of blood products in order to restrict their use.

Assignment 3

Implementing the precautionary measures previously recommended by the SHC suffices to guarantee maximum security without endangering either the supply of blood or self-sufficiency. These dispositions also hold for cell, tissue or organ donors.

Assignment 4

The precautionary measures that apply to healthcare professionals are described in the brochure "Recommandations pour la prévention de la transmission des encéphalopathies spongiformes transmissibles (maladie de Creutzfeldt-Jakob) en milieu hospitalier" (i.e. “Recommendations on preventing the transmission of transmissible spongiform encephalopathies (Creutzfeldt-Jakob disease) in medical facilities”).

The actual risk of variant Creutzfeldt-Jakob disease (vCJD) transmission through the transfusion of plasma derivatives of human origin

1. **Introduction.**

The emergence of variant Creutzfeldt-Jakob disease (vCJD) appears to have been caused by the carrying over of the agent responsible for bovine spongiform encephalopathy (BSE) to humans via contaminated food. Exposure to this food was at its greatest in the United Kingdom, which as a result has been faced with a considerably higher number of vCJD-cases (> 150 patients) than any other country. Outside the United Kingdom, a few countries have reported an isolated case of the disease, but France has counted around a tenth of the number of cases in the United Kingdom. Apart from the measures that have been taken to stop food-borne contamination, numerous countries have introduced precautionary measures against any potential secondary transmission that may occur during medical or dental care or that may be caused by blood transfusion and tissue or organ transplantation.

As regards blood transfusions, the plasma of donors from the United Kingdom has no longer been fractionated since 1998, the plasma derivative lots generally being very substantial, which in turn results in considerable logistical problems during their recall. In addition, models of the transmission of the vCJD-agent through plasma derivatives (references g and h) differ depending on the infectivity hypotheses used as well as on whether or not different infectivity reduction factors are taken into account.

According to British experts, haemophiliacs who have received coagulation factors were “at risk” (reference g), whilst the French experts take the view that haemophiliac patients have not reached the “threshold for infectivity” (reference h). It needs to be pointed out that the calculations made by the British authorities do not take into consideration any factors that reduce infectivity through partitioning or retention during the fractionation of plasma derivatives. The plasma of French donors is still being fractionated into plasma derivatives.

The SHC has issued several advisory reports in recent years that aim at containing the transmission of pathogens, such as prions. As regards the vCJD-agent, these advisory reports should be looked upon as precautionary measures, not a single case of vCJD having occurred in the Belgian population yet.

As there is no vCJD-agent inactivation method available that can be applied to blood products, measures pertaining to the eligibility of donors and the security of blood components have been taken to reduce the risk.

SHC advisory report no. 8048/5 thoroughly revises the value of the criteria used to exclude blood donors as well as the known characteristics of prion infectivity for different blood products in an attempt to ensure the security of blood products of human origin, and especially the security of plasma derivatives. The precautionary measures recommended by the SHC aim at countering the following risk factors: exclude donors with a family history of CJD, who have received a treatment with hormones extracted from human hypophyseal tissue or who have received a cornea or dura-mater transplantation, and avoid the use of plasma pools. A precautionary measure was added that is specific to the vCJD-agent, viz. excluding any individual from donating blood who has stayed in the United Kingdom for a total period of 6 months or more between 1980 and 1996.

Following the discovery of a first likely case of vCJD-transmission through non-leucodepleted blood in Great-Britain in 2003, the SHC also recommended the full leucodepletion of all blood components (SHC 8048-4). In addition, the SHC takes the view that there should be a permanent exclusion for donors who have received a transfusion of blood components in the United Kingdom after 1980 (SHC 8048/5).

2. Determining the actual risk of vCJD-transmission related to the use of plasma derivatives.

Analysing the risk of transmitting the vCJD-agent through the administration of plasma derivatives must take into account numerous factors. This is particularly true for the following:

1. its prevalence according to the geographical origin of the donors;
2. the efficiency of the questionnaire that is used for the selection of donors (the deferral criteria introduced as a precautionary measure and the adjustment of these criteria in the course of time);
3. the relative infectivity of the various blood products;
4. the reduction of the infectivity as a result of the different fractionation steps (precipitation, partitioning, purification);
5. the use of plasma derivatives.

Yet as far as the vCJD-agent is concerned, the actual risk is difficult to assess, as we do not have sufficient data at our disposal on the following factors:

1. the minimal infection titer;
2. the duration of the incubation period (asymptomatic phase);
3. the vCJD-agent quantity in the blood or plasma;
4. the fluctuations in the level of infectivity depending on the status of disease;
5. the actual infectivity depending on the type of blood product;
6. the varying infectivity reduction for each step in the preparation of plasma derivatives;
7. the types and quantities of the derivatives administered to each patient.

For the purposes of the present advisory report, the SHC reviewed the data from the scientific literature as well as certain internal reports from the plasma fractionation companies (references b-h), in order to assess the efficiency of the separation techniques in reducing or eliminating the infectivity linked to the presence of prions. The SHC finds on the basis of its assessment of these data that “spiking studies” use a variety of forms of the transmissible spongiform encephalopathy agent ('brain homogenate', microsomes, PrP^{sc}, …) as well as different detection methods (Western blot, bioassay, …). These experiments indicate that most plasma derivatives undergo steps that reduce their infectivity during fractionation. The reduction thus obtained in the experimental simulation of albumin fractionation is considerable (over 4 Log_{10} for certain steps).

Given the numerous uncertainties mentioned above, the SCH takes the view that though very low, the actual risk of transmission cannot be excluded, and is impossible to quantify.

This resulted in the SHC recommending that full traceability from the donor to the recipient and vice versa be made obligatory for all plasma derivatives except those that are used as excipients. Indeed, at present, such traceability only exists from the donor to the final product and vice versa. In contrast, it cannot be guaranteed or is even impossible between the recipient and the administered product. Indeed albumin presents the lowest risk as an excipient. As an additional advantage, it can be administered in small quantities.

As a result, the SCH recommended in its advisory report no. 8048/3 that a specific risk analysis be carried out for each individual method used in the preparation of plasma derivatives. The EMEA published recommendations on this subject for manufacturers (reference d), whilst reminding that no definitive guidelines can be provided at present.

3. Measures concerning the patients that need to be treated.

The SHC emphasizes the importance of carefully selecting the indications for the use of blood products in order to restrict their use.

4. Measures concerning the blood, organ, tissue and cell donor candidates who are believed to have received such products.

The measures that need to be taken with respect to blood donor candidates are mentioned under sections 2 and 3, as well as in SHC advisory reports no. 8048, 8048/5 and 8048/3.

These dispositions also hold for cell, tissue or organ donors.

5. Assessing the consequences of these patients for healthcare professionals such as doctors, surgeons, dentists and nurses.

The precautionary measures that apply to healthcare professionals are described in the brochure "Recommandations pour la prévention de la transmission des encéphalopathies spongiformes transmissibles (maladie de Creutzfeldt-Jakob) en milieu hospitalier" (i.e. “Recommendations on preventing the transmission of transmissible spongiform encephalopathies (Creutzfeldt-Jakob disease) in medical facilities”) (SHC 7276).

III. Composition of the working group that was involved in issuing this advisory report:

- Accoe Walter
- Baele Philippe
- Ballyn Geert
- Bontez Walter
- Cras Patrick
- De Mol Patrick
- Faber Chantal
- Ferrant Augustinus
- Gérard Michèle
- Lambermont Micheline
- Latinne Dominique
- Muylle Ludo
- Quoilin Sophie
- Renders Wim
- Sondag-Thull Danièle
- Thomas Isabelle
- Van Everbroeck Bart
- Verschraegen Gerda
- Voets Ellen

This working group is chaired by Mr. CRAS P., the scientific secretariat is carried out by Mr. HÜBNER R.

IV. References:

a) Letter from Mr. R. Demotte, Minister for Social Affairs and Public Health (with reference-), of 13/12/04 addressed to Mr. G. De Backer, Chairman of the SHC.
b) CPMP Discussion Paper «*The investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk*», November 2003, EMEA/CPMP/BWP/5136/03.
c) CHMP Position Statement «*Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products*», June 2004, EMEA/CPMP/BWP/2879/02/rev1.
d) CHMP «*Guideline on the investigation of manufacturing processes for Plasma-Derived Medicinal Products with regard to vCJD risk*», October 2004, EMEA/CPMP/BWP/5136/03.

Scientific references:

e) «*Removal of TSE agents from blood products*», Vox Sanguinis, Vol. 87 (Supplement 2):7-10, 2004.
f) «*Removal of Prions by Plasma Fractionation Processes*», Transmissible Spongiform Encephalopathies Advisory Committee, FDA, 10/02/03.
[http://www.fda.gov/ohrms/dockets/ac/03/slides/3923S1_13_files/frame.htm]
g) «*Risk Assessment of Exposure to vCJD infectivity in Blood and Blood Products*», February 2003, Det Norske Veritas Consulting.
[http://www.dnv.com/binaries/vCJD_Update_Report_tcm4-74414.pdf]
h) «*Evaluation du risque de transmission de l'agent de Creutzfeldt-Jakob par le sang et ses composants*», Actualisation Novembre 2004, AFSSAPS.

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