**FPS Public Health, Food Chain Safety and Environment**
**Superior Health Council**
Rue de l'Autonomie 4
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# Advisory report of the SHC on the risk of vCJD-transmission through the transfusion of plasma derivatives (SHC 8048/5).

(Validated by the Transitional Board on 9 November 2005)

## I. Request:

This advisory report is a revised version of SHC advisory report no. 8048/2, which bears the following characteristics (reference a):

On 21 November 2004, M. Bontez delivered a request for an advisory report from M. Cuypers to the SHC (cf. reference b) concerning the risk of variant Creutzfeldt-Jakob disease (vCJD) transmission through the transfusion of plasma derivatives made from plasma pools that contain the plasma of a blood donor believed to have contracted the disease.

This request was discussed during the meeting of the working group "Blood and blood products" that took place on 21 November 2004 in the morning. Nevertheless, the SHC decided to consult with the members of the working group "Inactivation of prions" before submitting an advisory report. The working group "Inactivation of prions" met on four occasions to discuss this topic (on 23 December 2004; 3 February 2005; 2 June 2005 and 1 September 2005). Meanwhile, an urgent provisional advisory report (SHC 8048/3) was issued on 23 November 2004 on a similar request received from the Minister's Cabinet. The SHC also received an additional request from the Minister's Cabinet on 13 December 2004 on the actual risk of vCJD-transmission through the transfusion of plasma derivatives of human origin (SHC 8097).

The provisional advisory report of the members of the working group "Inactivation of prions" was approved during the meeting of 1 September 2005 and validated by the SHC Board on 14 September 2005.

During the meeting of 8 December 2005, the working group "Inactivation of prions" approved a change that was made to SHC advisory report no. 8048/2 and added a reason for the recommendation that was made on traceability.

## II. Advisory report:

*Executive summary*

Assignment

1. Assess the proposal of excluding blood donors who might have been treated with plasma derivatives in order to reduce the risk of transmitting the vCJD-agent by administering these blood products.
2. Assess the need of implementing further precautionary measures in order to curtail the transmission of the vCJD-agent through blood transfusion.
3. Assess the communication strategy proposed, i.e. informing the medical profession in a broad sense.

Assignment 1

The Superior Health Council (SHC) has found that no other European country has implemented the exclusion of donors who have been treated with plasma derivatives. In addition, implementing the precautionary measures previously recommended by the

SHC suffices to guarantee maximum security without endangering either the supply of blood or self-sufficiency.

The SHC believes that there is no need to exclude donors who have been treated with plasma derivatives or to implement a permanent exclusion for donor candidates who have received a transfusion of blood components. Still, the SHC does take the view that a permanent exclusion is necessary for donors who have received a transfusion of blood components in the United Kingdom after 1980.

Assignment 2

The SHC regrets the lack of surveillance and traceability with respect to plasma derivatives in this country. At present, such traceability is only possible from the donor to the final product and vice-versa, whilst it cannot be guaranteed from the patient to the administered product and is impossible from the product to the patient. The SHC 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 3

The SHC takes the view that hospitals and blood establishments need to be made aware of the existence of a "CJD surveillance network". The SHC suggests that this network determine systematically which of its patients have received or donated blood products and that this information be exchanged with the relevant blood centre. A new information campaign may be of use to all doctors concerned.

*The risk of vCJD-transmission through the transfusion of plasma derivatives.*

**1. Introduction.**

Following the emergence of a second potential case of variant Creutzfeldt-Jakob disease (vCJD) transmission through blood transfusion in the United Kingdom (cf. reference g), several European countries have introduced additional precautionary measures in order to secure the supply of blood components and blood derivatives. This second case shows certain characteristics that lead to the conclusion that the risk of vCDJ-transmission through blood is probably higher than was believed to be the case up to now. Until now, all the patients who had developed the disease had been homozygous for methionine at codon 129 of the prion protein gene. Yet the patient in question was heterozygous and showed no symptoms of the disease. This raises the question whether individuals who are methionine heterozygous develop the disease after a very long incubation period, whether they contract a subclinical form of the disease or whether they are entirely resistant to it. Taking into account this finding, the situation needs to be reassessed, given the fact that the majority of the population carries the heterozygous genotype.

Conversely, the fact that the faulty prion proteins are only found in the spleen and lymph nodes, rather than in the tonsils or the lymphatic tissue of the intestine, suggests that in this case the infection may have been of intravenous rather than oral origin. Still, there is no absolute certainty that this is indeed a case of transmission through blood components rather than a case of food-borne contamination.

The data on both likely cases of blood transfusion induced vCJD-transmission between humans (in the United Kingdom in December 2003 and July 2004) only concern transmission through the transfusion of red blood cell concentrates, i.e. through cellular components.

In order to take up the challenge posed by infectious diseases and reduce the potential threat they represent for the security of blood and blood products, the SHC has issued several advisory reports in recent years that aim at countering any potential transmission of pathogens through blood transfusion.

Even though not a single case of vCJD has occurred in the Belgian population yet, this possibility cannot be excluded. Therefore, these advisory reports are to be looked upon as precautionary measures.

All the advisory reports issued by the SHC that are concerned with containing the transmission of pathogens through blood transfusion remain justified as a means of guaranteeing maximum security without endangering either the blood supply or self-sufficiency.

At present, several exclusion criteria for donors reduce the potential transmission of vCJD to an absolute minimum in Belgium.

1. *Precautionary measures that are specific to the vCJD-agent.*

Any individual who has stayed in Great Britain for a total period of 6 months or more between 1980 and 1996 is excluded from donating blood (SHC 4818).

Following the discovery of a first likely case of vCJD-transmission through the transfusion of non-leucodepleted blood in Great Britain in 2003, the SHC recommended the full leucodepletion of all blood components (red blood cells, platelets and plasma for transfusion (CSH 8048-4). The Royal Decree of 1 February 2005 guarantees that blood components systematically undergo leucodepletion.

2. *Precautionary measures related to prion diseases.*

Blood donations are excluded from:

- persons who show signs of Creutzfeldt-Jakob disease as well as the members of their family,

- donors who have received a treatment with hormones extracted from human hypophyseal tissue,

- individuals who have received a cornea transplantation,

- donors who have received a dura mater transplantation,

- individuals who have had a craniotomy,

- persons who have received an allograft of tympano-ossicular chains.

*3. Measures that aim at reducing the spread of pathogens.*

The blood components that are delivered to hospitals come from donations made in Belgium only (self-sufficiency).

As early as 2002 (SHC 7662), the SHC recommended that virus-inactivated fresh plasma no longer be prepared with plasma-pools: instead, the virus-inactivated fresh plasma should be subjected to virus-inactivation per individual unit. Indeed, the use of pools increases the number of recipients who may be affected by the presence of an infected donation in the pool (SHC 8093).

## 2. The need and the efficiency of excluding blood donors who may have been treated with plasma derivatives.

As a precaution, certain European countries, such as France, the United Kingdom, Ireland, Portugal, the Netherlands and Switzerland, have excluded donors who have received a transfusion of blood components (reference c and d). Conversely, no country has implemented the exclusion of donors who have been treated with plasma derivatives. In Belgium, some 8,2% of donors answer “yes” to the question whether they have once received a transfusion of these components. The Royal Decree of 1 February 2005 stipulates that the current exclusion period for blood component donations is 6 months, or 4 months at least if NAT testing for hepatitis C is negative. This measure aims at preventing the transmission of viruses like HCV.

In its advisory report (SHC 8048-4) on the risk of blood transfusion transmitted vCJD, the SHC suggested that a risk assessment be carried out. Amongst other things, this risk will depend on the nature of the product. Plasma derivatives are looked upon as the blood products with the smallest potential risk of inducing the transmission of the vCJD-agent. Indeed, the infectivity of plasma is similar to that of cellular components, which contain leucocytes, but its fractionation involves additional purification steps (references e-f and h-k). In Great Britain, hundreds of haemophiliac patients were exposed to coagulation factors made from a plasma pool that contained the plasma of donors who carried the vCJD-agent. Yet until now, none of these haemophiliacs has developed the variant Creutzfeldt-Jakob disease.

The SHC does not recommend excluding donors who have been treated with plasma derivatives, the infectivity of the vCJD-agent being very limited for these derivatives. The methods used for preparing plasma derivatives involve several steps that remove the vCJD-agent. In addition, thus excluding donors would reduce the number of available donors to such an extent that this would result in problems in the blood supply. Moreover, donors are not always aware of their having been treated with such products. They do not always know that products such as anti-tetanus immunoglobulin are in point of fact plasma derivatives.

The only study that assessed the efficiency of excluding donors who have received a blood component has shown that this would only result in the prevention of a single

vCJD-case over a ten-year period in Germany (with a population of 80 million) (see reference l).

As a result, the SHC does not believe that there is any indication to exclude donors who have been treated with plasma derivates, nor that there should be a permanent exclusion for donor candidates who have received a transfusion of blood components. Nevertheless, the SHC does take 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.

**3. The need of implementing additional precautionary measures to curtail the transmission of the vCJD-agent through blood transfusion.**

At present, not a single case of vCJD or sporadic CJD transmission through plasma derivatives has been reported amongst haemophiliac patients. Yet these patients have been under narrow surveillance in several countries ever since the tragic incidents in which blood products were contaminated with HIV-1 and HCV. Constant haemo- and pharmacovigilance seems to be of crucial importance to identify any potential transmission. Unfortunately, the traceability of plasma derivatives can no longer be guaranteed as a result of their being delivered by hospital pharmacies as medication.

Consequently, the SHC recommends 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 from the patient to the administered product and is impossible from the product to the patient. Indeed, albumin presents the lowest risk as an excipient. As an additional advantage, it can be administered in small quantities.

**4. The value of the communication strategy proposed: informing the medical profession.**

The SHC takes the view that hospitals (doctors of the department of hospital hygiene, sterilisation departments, ...) and blood establishments need to be made aware of the existence of a “CJD surveillance network”.

Given the fact that this network does not systematically check which CJD patients have donated or received any blood products, the SHC suggests that from now on this information be collected and exchanged with the relevant blood centre.

A new information campaign may be of use to all doctors concerned.

## 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) « *Advisory report on the risk of vCJD transmission through the transfusion of plasma derivatives» (SHC 8048/2).*
b) Letter from Mr. D. Cuypers, Chairman of the FPS Health, Food Chain Safety and Environment (ref. DC/CDC/WB/0404), dated October 16th, 2004 and addressed to Mr. G. De Backer, Chairman of the SHC.
c) Survey EC Public Health and Risk Assessment « *Precautionary measures against vCJD transmission by blood* », European Commission Health and Consumer Protection Directorate-General, October 2004, 13 pages.
d) Press release «*Durcissement des critères applicables aux dons de sang »,* Swissmedic Journal, Vol. 8:763, 2004.
e) 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.
f) CHMP Position Statement «*Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products*», June 2004, EMEA/CPMP/BWP/2879/02/rev1.

**Scientific references:**

g) Article «*Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient*» Lancet, Vol. 364:527-529, 2004.
h) Article «*Factor VIII and transmissible spongiform encephalopathy: the case for safety*» Hemophilia, Vol. 8:63-75, 2002.
i) Article «*Removal of TSE agents from blood products*» Vox Sanguinis, Vol. 87 (Supplement 2):7-10, 2004.
j) Article «*Impacts and Concerns for vCJD in Blood Transfusion: Current Status*» Current Molecular Medicine, Vol. 4:361-373, 2004.
k) Article «*The modern landscape of transfusion-related iatrogenic Creutzfeldt-Jacob disease and blood screening tests*» Current Opinion in Hematology, Vol. 11:351-356, 2004.
l) Paper « *Modelling of effects of the exclusion of transfusion recipients*» TSE - Safety of Blood Components Meeting, PEI, 21/03/03. [ e-mail from Prof. Klaus Dietz to the scientific secretariat of the SHC]

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