The Synthesis Report on the public consultation of the SCENIHR opinion on

The Safety of Human-derived Products with regard to Variant Creutzfeldt-Jakob Disease

EXECUTIVE SUMMARY

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This report provides an overview on the comments and recommendations of various stakeholders, received during the public consultation of the SCENIHR opinion on the Safety of Human-derived Products with regard to Variant Creutzfeldt- Jakob Disease (vCJD). The on-line consultation took place from 22 December 2005 to 10 February 2006.

The objective of the SCENIHR consultations is in general to foster involvement of various interested parties and solicit comments on the SCENIHR opinions. This will ensure the wider understanding and use of the SCENIHR recommendations as well as facilitate timely identification of issues of concerns to stakeholders.

With regard to the vCJD opinion, the responding stakeholders included representatives of public authorities (incl. manufacture of medicinal products derived from human blood as well as users of human-derived products) and other organisations representing public authorities at European level. Comments were received both on-line and in letters differing to some extent from the format designed for the Internet consultation. The comments received were taken into consideration in the preparation of this report.

This document outlines stakeholder proposals for the further development of the vCJD risk assessment. The feedback on the SCENIHR opinion from stakeholders was constructive, but highlighted concerns especially in regard to the method used for the risk quantification. The stakeholders gave strong support for further development of the risk assessment methods and methods and validation mechanism of vCJD contamination at the European level.

The main points of the responses and specific recommendations from the public consultation have been presented in a concise manner. This report summarises the proposals and provides responses to the stakeholder proposals. The SCENIHR has also modified its opinion in order to better correspond to the stakeholder concerns. The Commission services will further consider how to take into consideration the issues related to international co-operation which were raised in the consultation, but which are not included in the SCENIHR mandate.

1. Background

Variant Creuzfeldt-Jakob Disease (vCJD) is a human version of the mad cow disease. Typical for this incurable neurodegenerative disorder is a very long incubation period of several years. During this period asymptomatic vCJD infected individuals in the population may cause secondary transmission of the disease.

The European Parliament and Council directives on Blood Safety (2002/98/EC), Tissues and cells (2004/23/EC) and on Medical Devices (93/42/EEC) ensure that the necessary control systems for disease prevention are in place and well implemented. In 2004 two vCJD cases were reported indicating the possible secondary transmission of vCJD by blood transfusion. In response to the request from the Commission, the independent experts of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) were requested:

1. To review the previous scientific SCMPMD Opinion on the 'Safety of Human- Derived Products with regard to TSEs' adopted on 18 January 2002, and the SCMPMD Opinion on 'Quality and Safety of Blood' adopted on 16 February 2000 in order to quantify, if possible, the nature and magnitude of the risks of transmission of the vCJD agent through blood donated by preclinical cases of vCJD, through surgical instruments or by instruments used in invasive procedures,
2. To evaluate the risk of vertical transmission of vCJD in pregnant women and
3. To evaluate the risk of vCJD transmission by the tissues stored in umbilical cord cell banks.

The SCENIHR opinion[1] concluded that the risk for vCJD transmission via blood and surgical instruments exists, but no routine vCJD screening methods are available yet. The SCENIHR also highlighted that there is a need for the development of appropriate tests for vCJD and validation system of forthcoming test methods at the EU level. The optimisation of transfusion practices and a good maintenance of the current regional blood supply systems were considered important for the minimisation of the potential transfers of vCJD contamination. Special treatments were considered necessary for surgical instruments. No risk for vertical transmission in pregnant women and from tissues stored in umbilical cord cell banks was considered probable.

The potential vCJD contamination via blood or via surgical instruments may concern the quality of life of European citizens. The SCENIHR opinion provides a comprehensive and careful review of the potential risk of vCJD transmission. It allows the Commission and public authorities in Member States to assess the adequacy of existing procedures and technical requirements and indicates areas of further research and development.

The priority for the Commission is to ensure a high level of safety for citizens in relation to blood establishments, hospitals and in umbilical cord cell banks. Therefore the SCENIHR, in order to ensure that the potential concerns of stakeholders' are sufficiently addressed, decided to launch a public consultation on the opinion.

[1] SCENIHR/03/2005

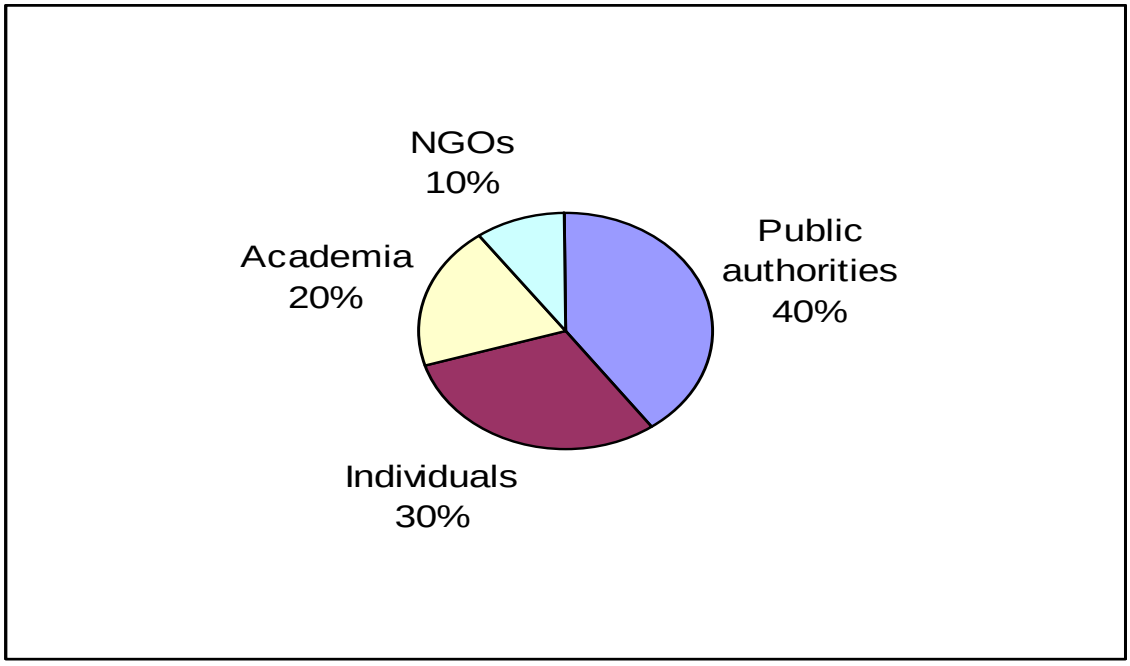
2. Public consultation

2.1 Responses to the Consultation

On 16 December 2005 the Commission, in consultation with the SCENIHR, launched a public consultation on the SCENIHR opinion on 'the safety of human-derived products with regard to variant Creutzfeldt-Jakob Disease'. The objective of this consultation was to collect views of various interested parties with regard to the scientific opinion.

A total of 10 contributions were received from public authorities, individuals, academia and NGO. The public authorities and academic institutions refer to institutions working closely with blood safety issues in Member States or at the European level.

Figure 1. Responses to the public consultation – Stakeholder groups



All the contributions were received from the EU countries: 2 from France, Netherlands and United Kingdom and 1 from Greece, Finland, Germany and Sweden.

This report provides a synthesis of the positions most frequently advanced by respondents with regard to the SCENIHR opinion. It does not reflect any judgement on the part of the SCENIHR as regards the different comments made in response to the consultation. In drawing up this summary, the SCENIHR has been guided not only by the number of respondents expressing a particular point of view, but also by qualitative considerations such as the extent to which the respondents are representative and the arguments advanced by respondents in support of their views. For this reason, the report does not present a systematic statistical analysis, but rather a qualitative assessment of the responses received and of the main arguments underpinning these responses. What follows, therefore, should be regarded as a summary of statements provided by respondents in respect of their perceived priorities on the issues covered in, or relating to, the Consultation Document.

2.2 Key issues arising from the public consultation

2.2.1 Potential risk for vCJD transmission via blood donation and surgical instruments

The SCENIHR stated in its opinion that

"The general conclusions and recommendations of the previous Opinions on the safety of human derived products including blood and blood components are still valid. Research on detection methodology has further evolved and an update is presented. Two aspects need our current attention; the possibility of transmission of vCJD by blood and blood components, and the presence of vCJD infected individuals in the population. The possibility for transmission by blood or blood products seems likely in view of the two cases of vCJD infection in persons who received previously a blood donation. In addition, the UK study evaluating anonymised routine appendicectomy samples (Hilton at al, 2004) indicates that vCJD infectivity may be present in the UK population at higher levels than the present numbers of identified clinical cases suggest.

There is a risk that a vCJD infected donor could pass infective material to one or more recipients of blood and blood components. In the worst case scenario each therapeutic unit of blood donated could contain as much as 4500 infectious units.

In view of the distribution of vCJD infectivity over the various blood compartments leucodepletion may produce no more than a 25% reduction in infectivity. Based on the data of the UK appendix study and the worst case scenario, and taking into account the population eligible for blood donation, the number of donations and the percentage of the population actually donating blood, up to 1250 infected donations may occur, per year, in the UK.

If there are 1250 infected donations per year they will result in 3750 new infections each year in the UK assuming that donations are typically split between 3 recipients. Of these 3750 new infections the subgroup living long enough after the transfusion to develop vCJD is approximately 50 %, so 1875 new individuals are eventually expected to develop vCJD. However, this worst case scenario does not fit the current data on vCJD case trends in the UK and may therefore largely overestimate vCJD transmission. It is unknown how vCJD may develop in heterozygotes at codon 129 of the PRNP gene. They may be not susceptible for developing clinical vCJD, but also could have a prolonged incubation period. Regarding sustainance of such a vCJD infection in the population by blood transfusion, preliminary data from one mathematical model suggest that it is unlikely that a vCJD infection could establish itself in the population by blood transfusion only.

The risk assessment is directly applicable only to the UK situation. In order to perform similar risk assessments for other Member States, it is recommended that data are collected on the presence of infection (PrP^{Res}) in the general population similar to the UK appendix study.

The current decline in the onset of clinical vCJD in the UK and the general low number of cases in the older age groups that comprise the majority of blood recipients, strongly indicate that this worst case scenario considerably overestimates transfusion-related vCJD disease development.

There are several potential explanations, namely

- *infections may have a very long incubation period so that the individual dies before disease develops,*
- *infections in some groups such as the MV heterozygotes may not be associated with blood infectivity,*
- *different genotypes may not transmit efficiently to each other even if the unit is infectious.*

Taking the lower limit of the confidence interval of the prevalence from the UK appendix study and assuming that only ten percent of infectious donations actually transmit the infectious agent, the number of infections resulting would be 9 per year in contrast to the 1250 predicted by the worst case scenario. Independent of the method of calculation transmission by blood transfusion may occur. Based on current data, the frequency cannot be reliably estimated, but even in the UK it is low. The frequency is largely dependent on the number of asymptomatic infected individuals in the general population which is likely to differ from one Member State to another.

There is no evidence that individuals working in hospitals have developed vCJD by virtue of their occupation. Transmission of TSEs during surgical procedures remains a concern, but to date there is no evidence that it has actually occurred in relation to vCJD. To minimize the risk of transmission of vCJD by surgical instruments procedures are recommended based on the probability of the patient under investigation/treatment being infected with vCJD (or any other TSE).

- *For clinical vCJD patients potentially contaminated instruments must be destroyed.*

- *For patients at high risk single use instruments are recommended, alternatively cleaning plus chemical inactivation plus physical inactivation, or cleaning plus chemical inactivation or physical inactivation may be used, depending whether the treatment is an activity with high or low risk, respectively.*

- *For patients not deemed to be at risk for TSE cleaning plus chemical inactivation or physical inactivation, or cleaning plus classical disinfection or sterilization may be used, depending whether the treatment is an activity with high or low risk, respectively.¨*

The views of the respondents divide in regard to nature and magnitude of risk of transmission of vCJD through blood donation and surgical instruments. The respondents criticise the risk calculation method on a worst case basis.
The key remarks to the SCENIHR opinion are the following:

- International consensus and scientific peer review on the assumptions and the interpretations of available biological data are needed.
- Further work is needed on different risk assessment models applied internationally and cooperation should be encouraged between experts on blood, TSE and risk analysis as well as public health authorities and governmental representatives [EBA]
- Requirements for possibly additional safeguards for blood components and risks of plasma products to be assessed [EBA]
- Third case of vCJD by blood donation should be included [EMEA]
- Although the transmission efficiency of blood donation is not known, the accumulating evidence suggests that blood donation is an efficient route of vCJD transmission [EMEA]

- The worst case scenario applies the limited data of animal studies where robust experiments to examine infectivity in blood through the incubation period of TSE infections were not done [SEAC].
- The estimation is based on limited age group: prevalence of the vCJD infection outside this group is poorly known and may be underestimated [SEAC]. The risk of vCJD transmission is related to the prevalence of the vCJD infection in the donor population that varies from one country to another and that is not known [EMEA]. It is too early to make any conclusions on the transfusion-related vCJD cases since the possibly existing subclinical and pre-clinical cases due to secondary transmission are not known. [EMEA, RIVM}.
- Further clarifications are needed on number of infections: one donation may lead to more than one infection since blood can be split between a number of individuals, one

recipient receives more than one product and some patients (neonates and TTP) receive multiple transfusions [SEAC, EBA]

- Susceptibility of MV or VV genotypes to vCJD infection may explain only part of the discrepancy between the worst case scenario and the actual infection situation and may be due to large variety of reasons [SEAC]
- Secondary infection routes should be taken into account as they interact on the risk of further transmission [EBA]
- Persistence of vCJD infection in the population cannot be evaluated with one and unpublished model results [SEAC]
- The method used is not peer reviewed and should not set a standard for the assumptions for risk models [EBA]. According to the WHO and EMEA meetings in 2005, the UK modelling did not reach the same conclusions as the German model. Surgery and dentistry are additional fields that ought to be included into such modelling [EMEA].

- Further clarifications would be necessary in regard to treatments of surgical instruments and patients at high risk [SEAC, EBA]
- No data exists on the occupational exposure to vCJD/BSE: therefore no conclusions in regard to that can be made [SEAC].
- The potential of surgery to give rise to a secondary vCJD has not been discussed [SEAC] An instrument exposed to high levels of infectivity from the brain or spinal cord cannot be reused even after reprocessing under stringent conditions [RIVM].
- Single-used instruments may not be available for all surgical operations and separate advice should be given regarding specialist equipment [RIVM].

- Important caveats such as amounts of vCJD agent in blood, prevalence of subclinical vCJD could have been highlighted in the text [SEAC]
- Further research on the prevalence of sub-clinical vCJD infection necessary [SEAC]
- The model uncertainties should be weighted against the benefits and the negative effects of the proposals [EBA]

2.2.2 Potential risk of vertical transmission of vCJD in pregnant women

The SCENIHR stated in its opinion the following:

'There are no proven instances of vertical transmission of any human prion disease. The available animal data are inadequate to allow firm conclusions concerning vertical transmission to be drawn. It is recommended that there is a follow-up for children that are born to mothers who had or developed clinical vCJD. There are no data indicating that breast milk transmits human prion disease.

As regards the vertical transmission, the stakeholder views agree or mostly agree with the SCENIHR opinion. The reservations given by stakeholders relate mainly to the scarcity of studies that do not give a strong justification to state that there is no vertical transmission.

The respondents highlighted notions in regard to the following issues:

- The available animal data is inadequate to allow firm conclusions on vertical transmission, but absence of evidence is not evidence of absence [EBA, RIVM]

- Small number of infants born to mothers incubating vCJD during gestation do not facilitate conclusions about non-existence of the risk for vertical (or horizontal) transmission [SEAC, EMEA, RIVM].
- The data on transmission via breast milk may not be directly applicable to vCJD as the distribution of infectivity in peripheral tissues is greater [SEAC, EMEA].
- Further studies on the follow-up of children born to mothers with vCJD is important [SEAC]. Active follow-up of children born to mothers with vCJD may be even unethical and the benefits need to outweigh the risks and side effects [EBA].
- Experiments with humanised mice to study vCJD transmission in utero and/or via lactation [SEAC]

2.2.3 Potential risk of vCJD transmission by the tissues stored in umbilical cord cell banks

The SCENIHR stated in its opinion that:

Current data do not indicate that prion infectivity is transmitted by cord blood cells.

The respondents highlighted the additional aspects important for the opinion:

- Lack of data on the vCJD infectivity in cord blood of infected mothers [SEAC]
- The recommendation is at odds with the present measure to exclude blood donors who have received a cornea transplant given the lack of evidence for transmission of classical CJD by blood [EBA].
- Little data is currently available to indicate whether or not prion infectivity could be transmitted by cord blood cells [EMEA].

2.2.4 Overall situation in regard to risk of vCJD transmission

The SCENIHR stated in its opinion that:

In conclusion, as long as there is a risk that infectious prion protein is present in blood and blood components, there will be a risk of transmission of vCJD disease by transfusion. Blood transfusion appears the most likely route for inter-human transmission of vCJD. The Committee does not consider that specific measures are needed to reduce the risk from vCJD infectivity in blood. However, it recognises that there are good practices to reduce any risk for transmission of infectious diseases such as optimal use of the transfusion to reduce the number of patients exposed, and optimal blood donation techniques and blood transfusion practices which minimize the number of blood donors to which an individual patient is exposed.

Respondents propose the following additional aspects to be considered in the overview:

- Clarification needed for the text on transmission from blood transfusion [SEAC]
- Specific measures needed to reduce the risk from vCJD infectivity in blood [SEAC]
- Research for appropriate routine screening methods for vCJD is needed [SEAC]
- Blood transfusion cannot be considered the most likely route if neither surgery, dentistry, transplants of organs, tissues, cells and cell derived products nor plasma products are evaluated [EBA, EMEA, RIVM]

- Guidance needed on how to estimate the geographical risk of vCJD transmission [EBA]
- Specific measures are needed such as donor exclusion, leucodepletion, import of fresh frozen plasma, reduction of plasma in blood components for transfusion, research on prion removal filters in addition to optimatization measures mentioned in the opinion [EMEA].

2.3 The SCENIHR responses to the comments

The SCENIHR thanks the stakeholders for the clear comments on the published vCJD Opinion. Most of the comments on rephrasing the text to clarify its intent have been accepted.

Considering the risk assessment, the data used are the data of the appendix-tonsillectomy study of Hilton et al 2004. The SCENIHR is aware of the limitations of the data which are the basis of the risk assessment made in the opinion. However, so far these are the only data available. Also the estimations on the development and the trend for this as it was described in the literature over the past years have been incorporated in the document. The risk assessment was based on the possible infection of all UK individuals independent of the genetic distribution at codon 129.

The SCENIHR did compare the estimation based on the data of Hilton et al 2004 in relation to the current development of vCJD in the UK and the discrepancy between these data. This discrepancy might be explained by several factors as described in the Opinion. The SCENIHR recognises the possibility for sub-clinical and dormant infections in the population.

The SCENIHR recognises that in view of the presence of vCJD it would be very difficult or almost impossible to perform similar studies to the appendix-tonsil study in other Member States of the European Union. An estimation based on BSE cases does also not provide the desired information, as can be seen by the UK estimates published over the years and presented in Figure 5 of the Opinion. However, data on BSE cases are probably the best alternative for vCJD data as the dietary exposure was found to be the most likely risk factor for vCJD (Ward et al 2006).

The SCENIHR recognises that the approach used in the opinion was not peer reviewed, and is an estimate of the SCENIHR where the worst case scenario was used and all the assumptions were clearly stated in the Opinion. The public consultation itself may be considered an open peer review process.

The SCENIHR recognises the need for more cooperation between the TSE experts and risk assessors. Already some actions in this respect have been initiated by EMEA and Health Canada

As regards surgical instruments and vertical transmission, the texts have been adapted for clarification. For surgical instruments the SCENIHR feels that this has been properly addressed. Although assessment of vertical transmission and the cord blood is based on limited data, so far as the SCENIHR is aware there have been no instances of vertical transmission. The text on vertical transmission has been also modified in order to highlight scarcity of studies or study material for the conclusions. Thus, so far there is no indication for vertical transmission.

The statement on measures to be taken to avoid transmission by blood donation has been modified in the text.

3. Conclusions

The public consultation brought out the demands related to the safety of human-derived products and potential transmission of vCJD via blood donation, surgical instruments, and cord cell banks and via pregnant women. It highlights safety demands for public authorities and specific needs for the further development of screening methods of the vCJD infected, preclinical cases and the respective need for European level validation system for those screening methods.

The consultation highlights the need for assuring the continuous maintenance of the existing regional system of blood establishments. Furthermore, despite the fact that stakeholders had different approaches and views to risk assessment and its international improvement, several points of convergence were identifiable.

The public consultation of the SCENIHR opinion sought stakeholder involvement and in doing so succeeded in obtaining useful advice both in regard to the current opinion and the future work in the field of risk assessment methodologies. Both are considered most valuable. Stakeholders views have been taken into account in the modified opinion and will be taken into account in the forthcoming work of the SCENIHR.