Variant Creutzfeldt-Jakob disease and blood transfusion

To the Minister of Health, Welfare and Sport

Subject	:	Presentation of advisory report on variant Creutzfeldt-Jakob disease and blood transfusion
Your reference	:	GMV/MHB 984171
Our reference	:	-3490/KG/ts/629-Z
Enclosures	:	1
Date	:	1 February 2001

Dear Minister,

In response to your request for advice (letter no. GMV/MHB 984171), I hereby present an advisory report on variant Creutzfeldt-Jakob disease and blood transfusion. This report has been produced by a Health Council committee specially created for this purpose and has been evaluated by the Standing Committee on Medicine and the Standing Committee on Infection and Immunity.

In an advisory report delivered on 8 February 2000 the Committee recommended the use of leukodepletion – irrespective of whether or not this procedure is desirable in connection with the transmission of variant Creutzfeldt-Jakob disease via blood or blood products. In the present advisory report, the Committee advocates the introduction of leukodepletion, also because of this possible transmission. In addition, it recommends that donors who have undergone a blood transfusion since 1985 should be rejected.

Yours sincerely,
(signed)
Professor J.J. Sixma

Variant Creutzfeldt-Jakob disease and blood transfusion

to:

the Minister of Public Health, Welfare and Sport

No. 2001/02E, The Hague, 1 February 2001

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature Preservation & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Contents

Executive summary

Prion diseases are fatal disorders in humans and animals that are characterised by degenerative changes in the brain. The current hypothesis is that they originate in the transformation of the normal cellular prion protein (PrP^{C}), which is expressed in various cell types, into abnormal prion protein (PrP^{Sc}, from scrapie, a prion disease occurring in sheep). The exact function of the prion protein is not fully understood. Since the 1980s, the United Kingdom has been afflicted by an epidemic of a previously unrecognised prion disease in cattle, known as bovine spongiform encephalopathy (BSE or "mad cow disease"), which has been detected in more than 175,000 cattle. Up until 22 January 2001, nine cattle with BSE had been identified in the Netherlands.

A prion disease that has long been known to occur in humans is Creutzfeldt-Jakob disease (CJD), which has a virtually stable incidence of approximately one per million person years. In 1996 a new variant of the disease (vCJD) was recognised in the United Kingdom. The incidence of vCJD appears to be increasing. Up until the 3rd January 2001 vCJD had been diagnosed in 88 patients, 83 of whom have died. In France there have been two deaths from vCJD. The disease has been identified in a third patient. It is unclear how the situation will develop in the United Kingdom and in the rest of Europe. Estimates of the total number of vCJD patients to be expected in the United Kingdom range from less than one hundred to many thousands. There is strong evidence to suggest that a single agent—herein referred to as the BSE agent—is responsible for both BSE and vCJD.

Concerns about the possible transmission of CJD and vCJD via blood and blood products have prompted various European countries to take precautionary measures.

One of these measures is leukodepletion, i.e. the removal of white blood cells from cellular blood products. Interest in leukodepletion as a precautionary measure arose following the detection of PrP^{Sc} in vCJD patients in lymphoid tissue such as the tonsil, which contains many white blood cells. The discussion which arose about the possible role of the so-called B lymphocyte (a type of white blood cell) in the transportation of prions to the brain reinforced this interest.

It is likely that the Dutch population (and therefore also the Dutch donor population) has been exposed to the BSE agent via the food chain. It cannot be completely ruled out that this exposure is still taking place. It is not possible to accurately quantify the degree of exposure of the donor population. Also the extent of exposure to the BSE agent required for an individual to become infected is not known. It is likely that comparatively more people have become infected in the United Kingdom than in the rest of Europe. Since it is possible that donors have been exposed to the BSE agent, and because PrP^{Sc} has been detected in lymphoid tissue, it is not possible to fully rule out the transmission of vCJD via blood or blood products in the Netherlands. However, an estimation of the risk of transmission cannot be made.

In recent years various measures have brought about a reduction in the risk of the BSE agent being transmitted from animals to humans. Nevertheless, two precautionary measures are recommended to reduce or prevent the possible transmission of vCJD via blood or blood products of human origin. The measures are the exclusion of donors who after 1985 have received a transfusion with a cellular blood product and the introduction of leukodepletion.

The emergence of vCJD in France is considered an illustration of the spread of the BSE agent across the European continent. It is expected that the reduction in the degree of exposure to the BSE agent that would result from the exclusion of donors who have stayed in the United Kingdom for a certain period would be so limited that there is no reason to recommend this measure.

Only limited scientific data could be included in this report. Research in a number of areas is therefore needed, such as the possibility of early recognition of infected individuals, the epidemiology of vCJD, and the relative importance of transmission of the BSE agent via blood and blood products in relation to the transmission via food. Because the proposed measures are based on precaution, development of scientific knowledge should lead to re-evaluation.

European harmonization at the introduction of precautionary measures is important in order to maintain international exchangeability of blood products.

Chapter **1**

Introduction

Being treated with blood and blood products is not without risk, and this is unlikely to change in the future. Blood transfusions can have negative effects on the recipient, such as the transmission of viruses, immunisation against HLA antigens and immune system inhibition. Although various measures have considerably reduced the chances of transmitting infectious agents such as the hepatitis B virus, the hepatitis C virus and HIV, such risks have not been totally eliminated. For other agents, including the transmitters of the so-called prion diseases, much less is known about the risk of transmission via blood or blood products. This recommendation deals with the chance of transmitting variant Creutzfeldt-Jakob disease, one of the prion diseases occurring in humans, and the precautionary measures to be taken in that regard.

1.1 Background

Prion diseases, characterised by degenerative changes in the brain, are fatal. The current hypothesis is that prion diseases stem from an irreversible change in the spatial structure of the normal cellular prion protein (PrP^{C}, from cellular) expressed in a number of cell types. The conversion of PrP^{C}, the precise function of which is not known, produces abnormal prion protein for which two abbreviations are used: PrP^{Sc} (after scrapie, a prion disease in sheep), and PrP^{RES} (after resistant, due to the insensitivity of the abnormal prion protein to enzymatic breakdown).

Prion diseases are mostly sporadic but can also be the result of familial or infectious conditions. The most common prion disease in man is Creutzfeldt-Jakob disease (CJD),

with an incidence of approximately one per million person years. Since the 1980s, the United Kingdom has been affected by an epidemic of bovine spongiform encephalopathy (BSE, 'mad cow disease'), a prion disease of cattle, that has been diagnosed in more than 175,000 animals. Over the past few years various measures have significantly decreased the number of new infections in the United Kingdom. In the Netherlands nine cattle with BSE have been identified as of 22 January 2001.

In 1996, a publication appeared in *the Lancet* describing ten patients with a variant of Creutzfeldt-Jakob disease (vCJD). In March 1996, the government of the United Kingdom made a statement on vCJD in connection with exposure to the BSE agent. Since that time there have indeed been strong indications that a single agent (referred to here as the BSE agent) is responsible for both BSE and vCJD. Up until 3 January 2001, vCJD had been identified in 88 patients in the United Kingdom, 83 of whom have died. In France the first vCJD patient died in 1996 and the second very recently. The disease has now been confirmed in a third patient. The fourth vCJD patient outside the United Kingdom is a woman in Ireland who lived in England for five years.

In anticipation of data concerning the transmission of CJD and vCJD via blood and blood products, various European countries have taken precautionary measures to keep the chance of infection as low as possible. One of these measures is leukodepletion, the removal of white blood cells from donated blood. The interest in leukodepletion as a precautionary measure against the transmission of vCJD is based on the fact that PrP^{Sc} has been demonstrated in the lymphoid tissue of vCJD patients. Such tissue, which includes the tonsil and the spleen, contains many white blood cells. The publication of research into the possible role of the B-lymphocyte (a type of white blood cell) in the transport of prions to the spleen and the brain has intensified this interest.

1.2 Request for advice

On 2 September 1998, the Health Council of the Netherlands received a request from the Minister of Public Health, Welfare and Sports for advice concerning the risk of transmission in man of vCJD via cellular blood products or via products prepared from plasma (annex A). On 5 January 1999, the President of the Health Council of the Netherlands installed the Committee that prepared the current recommendation (annex B).

1.3 Scope

The minister's first question is whether there is a chance of transmission of vCJD via blood or blood products. If the answer to this question is affirmative, the Committee will indicate whether it can give a reliable estimate of that chance and will address the

mechanisms on which such transmission might be based. The Committee will also discuss any appropriate precautionary measures.

The minister asked the Health Council to focus specifically on the leukodepletion of cellular blood products as a technique for countering the possible transmission of vCJD. It is with this goal in mind that leukodepletion has been introduced in the United Kingdom, Ireland and Portugal. In France, this method has been introduced to prevent immunisation against HLA antigens in the recipient and to profit from possible additional benefits in terms of virus transmission and immunomodulation. In the current recommendation, the Committee has decided to restrict itself to the issue of leukodepletion as a possible precautionary measure against the transmission of vCJD. In a previously issued recommendation the Health Council discussed other possible pros and cons of the general introduction of this technique.

1.4 Structure of this advisory document

In the following chapter, the Committee gives an overview of current knowledge concerning vCJD, taking the recommendation 'Prion diseases' issued by the Health Council in 1996 as a starting point. Chapter 3 concerns the risk of transmission of vCJD via blood and blood products. In chapter 4 the Committee discusses the possible precautionary measures to be taken.

Chapter **2**

Variant Creutzfeldt-Jakob disease

The recommendation on prion diseases, issued by the Health Council in 1996, contains an overview of these progressive and invariably fatal diseases in man and animals (GR96). That recommendation also exhaustively addresses the so-called 'prion hypothesis'. In this chapter, the Committee only cites developments concerning the variant of Creutzfeldt-Jakob disease (vCJD) referred to in 1.1.

2.1 The patients

In 1996, Will and colleagues reported on ten patients with vCJD (Wil96). In comparison with patients with the classic form of CJD, these patients were extraordinarily young and showed a different clinical and pathological picture. The definitive diagnosis 'vCJD' (definite case) was made on the basis of microscopic studies of brain tissue (Kre96). Since March 2000, there has also been registration of patients who probably have vCJD. These so-called probable cases include both the living patients in whom vCJD is suspected on the grounds of such factors as the clinical picture and, in some cases, molecular-biological studies of tonsil biopsies (Wil00), as well as deceased patients in whom the study of brain tissue has not yet been completed. Up until 3 January 2001, the total number of definite and probable cases in the United Kingdom came out at 88 (DoH01). Five of these patients were still alive at that time.

Until recently, only a single case had been described from outside the United Kingdom. This concerned a patient from France who was one of the first to die of vCJD (Cha96). It is assumed that he became infected by (self) injection with

contaminated cattle growth hormone (Ver98), but this assumption has not been officially confirmed. A second vCJD patient died in France very recently. According to the definitions utilised in the United Kingdom, a third French patient is a probable case. The French patients have never visited the United Kingdom (EC00a). The fourth vCJD patient outside the United Kingdom is a woman in Ireland who lived in England for five years.

Although the incidence of vCJD in the United Kingdom seems to be increasing (And00), it is not possible to estimate how many people will go on to develop the disease there or in the rest of Europe. Estimates of the total number of anticipated vCJD patients in the United Kingdom vary from a few dozen to many thousands (Cou97, Gha00). Such estimates are made more difficult by the fact that all of the patients studied to date belong to the same genetic subpopulation. The gene that codes for the prion protein shows variation in codons, the parts of genes that code for amino acids. One published English study of 106 Caucasian individuals, described two variants of codon 129 of the gene, that code for the amino acids methionine or valine. These variants result in three genotypes: homozygotic for methionine (37 percent of the study group), homozygotic for valine (12 percent), and heterozygotic (51 percent) (Col91). All vCJD patients studied thus far are homozygotic for methionine (Col99a). It is suspected that the prevalence of methionine homozygotes means that PrP^{C} transforms into PrP^{Sc} (see 1.1) more readily in these individuals than in others (Ray97). It is not clear whether vCJD will remain limited to methionine homozygotes or whether it can also occur in heterozygotes or valine homozygotes (possibly with a much longer incubation time or a different clinical manifestation). Other, still unknown, genetic factors may also be involved in the development of vCJD.

2.2 vCJD and BSE

The first report of a relationship between BSE and vCJD was based on an epidemiological fact: vCJD occurred in the country with by far the largest number of cattle with BSE (Wil96). In 1996 the Health Council called the connection between BSE and vCJD 'hypothetical' (GR96). Since then there have been strong indications that both disease pictures are caused by the same agent, referred to here as the BSE agent. For example the PrP^{Sc} of vCJD patients shows considerable parallels with that of cattle with BSE (Col96). In experimental animal studies, also, it is impossible to differentiate between the agents that cause vCJD and those that cause BSE. Monkeys to whom brain material from BSE cattle has been administered show brain abnormalities that correspond to the abnormalities seen in vCJD patients (Las96a). In experiments with mice, the injection of brain material from patients who died of vCJD led to a similar distribution of neuropathological abnormalities and death after

approximately the same time as the injection of brain material from BSE cattle (Bru97, Hil97a, Sco99). Injection of brain material from CJD patients or from sheep with scrapie, on the other hand, showed different abnormalities and incubation times (Bru97, Hil97a, Sco99).

2.3 vCJD and lymphoid organs

In 1997, Hill and colleagues published a report showing that the presence of PrP^{Sc} had been demonstrated in the tonsil of a patient who had died of vCJD (Hil97b). Recently the same study group reported that PrP^{Sc} had been found in various lymphoid organs from patients who had died of vCJD, such as tonsils, spleen and lymph nodes (Hil99). In those patients who died of CJD, however, this was not the case.

Studies into prion diseases in sheep show that abnormal prion proteins are found in tonsil tissue long before the animals exhibit the symptoms of scrapie (Sch96, Sch98). In BSE cattle, however, the agent cannot be detected in the lymphoid organs either during the incubation phase or during the phase of manifest disease. Hilton and colleagues reported that PrP^{Sc} had been detected in tissue from an appendix that had been removed eight months before the patient in question began to manifest vCJD (Hil98). The appendix also contains lymphoid tissue.

The government of the United Kingdom has decided to carry out studies into the infection level of the population. This will be done by analyzing tonsil and appendix tissue (that has been surgically removed and then stored) for the presence of PrP^{Sc} (see 3.2).

2.4 vCJD and white blood cells

For some time white blood cells have been thought to be involved in the transport of prions from the periphery of the body to the central nervous system (Fra70, Kit91, Las96b). The presence of the abnormal prion protein in lymphoid organs has reinforced this suspicion, since this suggests that prion proteins can be transported via blood or lymph (Hil99).

In 1997 Klein and colleagues reported that B lymphocytes are responsible for the transport of prions (Kle97). About a year later these researchers themselves overturned their conclusion (Kle98). At present it is not clear whether B lymphocytes play a role in the transport of prions. Some researchers have suggested that another type of white blood cell, the follicular-dendritic cell, is much more important (Col98, Kit91, Kle98). Recently Brown and colleagues published data that indeed point to this (Bro99a).

Chapter **3**

Chance of transmission of vCJD via blood and blood products

In this chapter, the Committee explains its views on the chances of transmission of vCJD via blood and blood products originating from the Dutch donor population. It defines the 'Dutch donor population' (hereinafter referred to as: donor population) as the group of people in the Netherlands that donate blood. The donor population also includes Dutch people of foreign origin or people of non-Dutch nationality.

First to be addressed in this chapter is the exposure of the donor population to the BSE agent. The committee sees exposure as a condition for a possible infection. Subsequently it explores this infection and the question of the risk of transmission of vCJD. Finally, it discusses research into the transmission of prion diseases via blood.

3.1 Exposure to the BSE agent

In view of the lack of scientific evidence concerning the exposure of the donor population to the BSE agent, the Committee can only make an estimate of the exposure. In that context it points to the following:

- The Dutch population, and therefore also the donor population, has probably consumed infected meat or infected meat products from the United Kingdom in the 1980s.
- It is estimated that dozens of infected cattle made their way into the food chain in our country.
- In the Netherlands meat and meat products are available from countries where there might be insufficient control over the infection of cattle or where risk material

such as brains and bone marrow have not been or are not totally removed from meat products. Meat products from countries where sufficient measures are taken can contain components originating from countries where insufficient controls take place.

- Residents of the Netherlands travel to countries where they have an increased chance of consuming infected meat (in the 1980s the United Kingdom, now other European countries). The level of such passenger traffic can be described as intensive.

The Committee feels that the donor population has probably been exposed to the BSE agent and that further exposure cannot be entirely ruled out. It feels that it is not possible to precisely quantify the influence of the various specified determinants, and thus the degree of exposure of the donor population. There is quite probably a difference in exposure between the United Kingdom and the rest of Europe, since the total number of infected cattle in the United Kingdom is estimated at nearly one million (And96). In the rest of Europe this figure is estimated to be a few thousand (Sch97).

3.2 Infection of the donor population

From 3.1 it follows that infection of people from the donor population cannot be ruled out, even if it is not known in what way and to how much BSE-agent one must be exposed in order to become infected (EC00b). It is not known how many infected people there are in Europe. Considering the difference in exposure between the United Kingdom and the rest of Europe, it is probable that more people have become infected in the United Kingdom.

Recent publications have shown that it is possible to test people for infection with the BSE agent (Hil97b, Hil98, Hil99). The test in question can be applied to lymphoid tissue from the tonsil and the appendix (see 2.3), for example, but not to blood. The government of the United Kingdom decided to commission research into the degree of infection of the population by analysing tonsil and appendix tissue (that has been surgically removed and then stored) for the presence of PrP^{Sc} (War98, Wil98). One of the objections to this plan was that the proposed study would not produce reliable estimates of the infection level (Gha98). To date, this study has found no PrP^{Sc} in any of the material examined (Iro00). The quantity of studied material (appendix tissue from 3075 patients and tonsil tissue from 95 patients) is, however, too small to justify conclusions concerning the degree of infection in the United Kingdom.

The committee is not aware whether there are plans for similar studies in other European countries.

3.3 Transmission of vCJD

The transmission of CJD via blood or blood products is considered to be improbable (Col99b, Dui98, EC98, Esm93, Hey94, Sul97). The occurrence of CJD in a few patients a shorter or longer time after the administration of blood or blood products is attributed to chance (Cre95, Pat98). With regard to the possibility of transmission of vCJD via blood or blood products, nothing is known at present. There are no reports of patients in whom such transmission is known to have taken place. For example, studies of the brains of haemophilic patients who died of other conditions than prion diseases showed that the administration of coagulant factors produced from the plasma of large numbers of donors did not lead to the presence of PrP^{Sc} or abnormalities characteristic of prion diseases (Lee98). In that study, the interval between possible infection by the BSE agent and the death of the patients (three to twelve years) was, however, relatively short for prion diseases. In those patients who received blood from donors who later developed vCJD (at least eight of the dead vCJD patients from the United Kingdom were donors) the disease has not (yet) manifested. The differences between CJD and vCJD concerning pathogenesis and demonstrability of PrP^{Sc} in lymphoid tissue make a separate analysis for vCJD necessary.

3.4 Research

Scientific data concerning the transmissibility of prion diseases via blood and blood products is scarce. It often involves experimental animal studies or studies in which PrP^{Sc} is added to blood originating from donors (the so-called spiking-experiments). Both the method by which the infectious material used in the experiments is prepared and that used to determine the degree of infection are the subjects of scientific debate. The results of such experiments with material originating from vCJD patients are only expected over a period of months to years (Bro99, EC00a).

Brown and colleagues have shown that after the administration of scrapie-PrP^{Sc} to human blood, most infectivity is found in the cellular blood fractions (Bro98). In addition, distribution experiments using the blood of mice infected with a human prion protein (adapted to mice) show that the greatest infectivity occurs in the so-called buffy-coat, the fraction of the centrifuged blood in which most white blood cells are located (Bro98, Bro99b). In other fractions, for example plasma, infectivity seems to be lower (Bro98, Bro99b, Tay00). During a recent meeting of the European Commission, Brown gave a summary of studies into the infectivity of prion diseases in blood (EC00c). In addition to discussing a number of publications, this summary contained references to ongoing

experiments which indicate that it is possible for prion diseases to be transmitted via blood.

The above-mentioned meeting of the European Commission was held to discuss the implications of a publication on the experimental infection of a sheep with BSE via blood transfusion (Hou00). The committee that prepared the advisory document at hand sees this publication, which relates to a study that is also still in progress, as an extra indication that the transmission of the BSE agent via blood cannot be ruled out. It is considered to be essential that the study be completed, in order for the value of this initial result to be assessed. However, the study in question still has several years to run (Hou00).

3.5 Conclusion

The Committee concludes that the donor population has probably been exposed to the BSE agent and that, therefore, the possibility of infection of the population cannot be ruled out. In view of the chance of infection and the fact that PrP^{Sc} has been demonstrated in human lymphoid organs, it believes that the transmission of vCJD via blood or blood products can also not be ruled out. Experts from other countries, including the United Kingdom and the United States, came to the same conclusion (DNV99, FDA98). The Committee believes that the results of experimental animal studies, which are sometimes quite tentative, also point to the possibility of transmission of prion diseases via blood or blood products.

At this time both the degree of exposure and the chance of infection cannot be quantified. The Committee can therefore make no statement regarding the chance of transmission of vCJD via blood or blood products of human origin.

Chapter **4**

Precautionary measures

The Committee based its assessment of precautionary measures to be taken against the possible transmission of vCJD via blood and blood products on the precautionary principle. This was necessitated by the lack of scientific data on the exposure and infection of the donor population and on the transmission of vCJD. The European Commission considers that the precautionary principle applies, where scientific evidence is insufficient, gives no conclusion, or is unreliable, while a tentative scientific evaluation indicates that dangerous consequences for the environment or for health require that measures be taken (EC00d). Measures taken in the context of the precautionary principle should be re-evaluated when more scientific knowledge becomes available.

The Committee feels it is of the greatest importance that the supply of blood be maintained at all times. Although not without risk (see 1.1), blood and blood products can after all be vital in the treatment of a patient. Given the danger of loss of donors, the Committee feels that the precautionary measures on the quality and safety of blood and blood products, to be discussed in this chapter, may only be applied if this does not compromise the blood supply.

4.1 Donor selection

In the Netherlands, in accordance with European Union regulations, certain groups of donors have already been ruled out to minimise the risk of transmission of CJD and vCJD. For example, family members of patients with CJD are refused, as well as people who have received hormone preparations originating from the human

hypophysis. The same applies to recipients of transplants from the cornea or the dura mater. Plasma originating from countries where vCJD has been identified (at the moment only the United Kingdom) may not be used as the raw material for plasma products. Incidentally this last measure was mainly taken because lots of plasma products are often quite large and recalling them involves considerable logistical problems.

The Committee focused on the sensibility and feasibility of the implementation of a number of additional measures.

4.1.1 Ruling out donors who spent a certain period of time in the United Kingdom

People who spent a period of at least six months in the United Kingdom between 1980 and 1996 are ruled out as donors in Canada and the United States. Both countries are considering extending this ban to other European countries. Canada has already done this for France.

The Committee feels that this measure would make no substantial contribution to reducing the chance of transmission of vCJD in our country. For example, the occurrence of vCJD in France (see 2.1) means that the condition is not restricted to the United Kingdom (and Ireland), but that it has spread to the European mainland. In addition, a French committee has studied what the consequences would be of ruling out donors. On the basis of the results of a questionnaire amongst 16,787 donors, the Committee calculated (assuming that in France the chance of exposure to the BSE agent is a twentieth of that in the United Kingdom) that exclusion of donors who between 1980 and 1996 spent a period totalling at least six months in the United Kingdom would reduce the degree of exposure in the donor population by 3.2 percent (Agu00). The above assumption, concerning relative risk, was based on data about the import of beef from the United Kingdom.

The (Dutch) Committee estimates that the chances of exposure in the Netherlands and France are on the same scale. Partly on the basis of data from a study executed by the Sanquin Blood Supply Foundation, into the stay of donors in the United Kingdom, it is concluded that in the Netherlands, ruling out donors on such grounds would also decrease the degree of exposure in the donor population by only a few percent. It finds that insufficient to recommend such exclusion. In Canada and the United States, the chance of exposure to the BSE agent via food is so much lower that, in those countries, the measure does indeed result in a reduction in the degree of exposure of the donor population.

4.1.2 *Ruling out donors who have received blood transfusions*

As evidenced in the above paragraph, the Committee is concerned about possible transmission of the BSE agent via blood or blood products. Although exposure to the BSE agent via meat or meat products currently causes more concern than possible exposure via blood, this situation may change. For example, if measures taken to reduce the chance of transmission of the BSE agent from animals to man via food have the desired effect. It is also possible that the transmission of the BSE agent from man to man, via blood, is more effective than from animal to man, due to the absence of a species barrier. The main point for concern of the Committee in this matter is the possibility of circulation of the BSE agent in man via blood or blood products. In man, such circulation took place in the past with the hepatitis C-virus, when no screening test was yet available for that virus (Poe91). To prevent such circulation of the BSE agent, the Committee advocates ruling out donors who underwent transfusion with a cellular blood product after 1985. It proposes limiting the exclusion to cellular blood products (red blood cells or blood platelets), because animal studies have shown that other blood products have a lower level of infectivity (Bro98, Bro99b).

The committee is aware that this measure can lead to a considerable loss of donors and may necessitate a recruitment campaign for new donors. It is understood that, in view of existing uncertainty about the chances of transmission of vCJD, such exclusion might lead to unrest and might undermine public confidence in blood transfusion in general. Nonetheless, it considers this measure to be necessary.

The committee is aware that ruling out certain donors, such as the donors for the programme of rhesus D-immunoprophylaxis, could seriously endanger the treatment of some groups of patients. It therefore recommends maintaining the donors essential for that treatment.

4.1.3 *Ruling out donors on other grounds*

The committee has focused on a number of other measures such as ruling out donors on the basis of familial conditions of the nervous system other than CJD, or ruling them out on the grounds of psychiatric problems. It feels that these measures would be difficult to effect particularly because the associated criteria cannot be sufficiently specified.

4.2 Screening of donors or donations

Because abnormal prion proteins have been shown to be present in tonsils (Hil97b, Hil99), this might provide a way of screening people for infection with the BSE agent. The Committee feels, however, that this method of donor screening is not practically applicable. There is also no data concerning the sensitivity and the specificity of the tests. In addition, because there is no treatment for the disease in question, the question remains as to whether it is ethically justified to have donors undergo this test, even if they wanted to. So the Committee presently advises against such a study amongst donors.

Until recently, research into tracing infected donations focused chiefly on the detection of PrP^{Sc} in the buffy-coat, referred to in 3.4. Although rapid progress is being made in this area (Sch99), the techniques in question are still insufficiently sensitive to identify infected donations. Very recently, Fischer and colleagues reported that PrP^{Sc} binds to plasminogen that occurs in plasma (Fis00). They suggest that this finding can be used to track down infected donations and to remove PrP^{Sc} from blood products.

4.3 Donation treatment

If the abnormal prion proteins concentrate in one of the fractions of blood, the removal of that fraction would lead to a decreased chance of infection. One measure used in this context is leukodepletion, the removal of white blood cells from blood.

To be able to assess the envisaged effect of leukodepletion, knowledge of the distribution of prion proteins between the various blood fractions is required. Although research in this area is still in a very early stage, the Committee feels that an important role can be assigned to white blood cells because:

- Experimental animal studies and spiking experiments have shown that more infectivity can be found in the buffy-coat and cellular blood fractions than in other fractions (Bro98, Bro99, Tay00). One focus for research into identifying infected donations is the detection of PrP^{Sc} in the buffy-coat (Sch99).
- PrP^{Sc} has been shown to be present in the lymphoid organs of vCJD patients (Hil99). There are many white blood cells in the lymphoid organs.
- White blood cells may be important in the transport of prions (see 2.4).

On this basis, the Committee is advocating the total leukodepletion of cellular blood products as a measure against possible transmission of the BSE agent. It sees this measure as a necessary addition to the removal of the buffy-coat that takes place in the Netherlands since the 1980s. The European Commission also considered the

introduction of the total leukodepletion of cellular blood products (EC00a). In a previously issued recommendation, the Committee advocated leukodepletion after weighing up what, in its view, were more conclusive pros and cons (GR00).

4.4 In closing

In its deliberations, the Committee found that very little relevant scientific data is available. It therefore advocates research in a number of areas. This might involve research into the possibilities of the timely identification of infected individuals, epidemiological research into the spread of vCJD, research into the relative significance of spread of the BSE agent via blood transfusion in comparison with spread via food, and research into the infectivity of plasma and the further removal of plasma from cellular blood products. Because the proposed measures are based on the precautionary principle, they should be reviewed when additional scientific knowledge becomes available.

In the introduction of measures to prevent the transmission of vCJD via blood or blood products, the Committee attaches great value to European harmonisation, in order to guarantee the international exchangeability of blood products.

The Hague, 1 February 2001,
for the Committee

(signed)

K Groeneveld,	ADME Osterhaus,
Secretary	Chairman

References

Agu00 Agut H, Alpérovitch A, Barin F, *et al.*. Révision des mesures de réduction du risque de transmission des ESST par les produits sanguins. Paris: Rapport du groupe d'experts réuni sous l'égide de l'Agence Française de Sécurité Sanitaire des Produits de Santé et de l'Etablissement Français du Sang, 2000.

And96 Anderson RM, Donnelly CA, Ferguson NM, *et al.*. Transmission dynamics and epidemiology of BSE in British cattle. Nature 1996; 382: 779-88.

And00 Andrews NJ, Farrington CP, Cousens SN, *et al.*. Incidence of variant Creutzfeldt-Jakob disease in the UK. Lancet 2000; 356: 481-2.

Bro98 Brown P, Rohwer RG, Dunstan BC, *et al.*. The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongiform encephalopathy. Transfusion 1998; 38: 810-6.

Bro99a Brown KL, Stewart K, Ritchie DL, *et al.*. Scrapie replication in lymphoid tissues depends on prion protein-expressing follicular dendritic cells. Nature Med 1999; 5: 1308-12.

Bro99b Brown P, Cervenáková L, McShane LM, *et al.*. Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans. Transfusion 1999; 39: 1169-78.

Bru97 Bruce ME, Will RG, Ironside JW, *et al.* Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 1997; 389: 498-501.

Cha96 Chazot G, Broussolle E, Lapras Cl, *et al.* New variant of Creutzfeldt-Jakob disease in a 26-year-old French man. Lancet 1996; 347: 1181.

Col91 Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. Lancet 1991; 337: 1441-2.

Col96 Collinge J, Sidle KCL, Meads J, *et al.* Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD. Nature 1996; 383: 685-90.

Col98 Collinge J, Hawke S. B lymphocytes in prion neuroinvasion: central or peripheral players? Nature Med 1998; 4: 1369-70.

Col99a Collinge J. Variant Creutzfeldt-Jakob disease. Lancet 1999; 354: 317-22.

Col99b Collins S, Law MG, Fletcher A, *et al.* Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. Lancet 1999: 353: 693-7.

Cou97 Cousens SN, Vynnycky E, Zeidler M, *et al.* Predicting the CJD epidemic in humans. Nature 1997; 385: 197-8.

Cre95 Créange A, Gray F, Cesaro P, *et al.* Creutzfeldt-Jakob disease after liver transplantation. Ann Neurol 1995; 38: 269-72.

DNV99 Anonymous. Assessment of the risk of exposure to vCJD infectivity in blood and blood products. Final report for the Spongiform Encephalopathy Advisory Committee and the Department of Health. Det Norske Veritas Limited 1999.

DoH01 Department of Health. Monthly Creutzfeldt-Jakob disease statistics. http://www.doh.gov.uk/cjd/stats/jan01.htm

Dui98 van Duijn CM, Delasnerie-Lauprêtre N, Masullo C, *et al.* Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. Lancet 1998; 351: 1081-5.

EC98 European Commission. Scientific committee on medical products and medical devices. Opinion on the risk quantification for CJD transmission via substances of human origin. Brussels: European Commission, 1998.

EC00a European Commission. Scientific committee on medicinal products and medical devices. Update of the opinion given by the scientific committee on medicinal products and medical devices on the risk quantification for CJD transmission via substances of human origin. Brussels: European Commission, 2000.

EC00b European Commission. Scientific steering committee. Oral exposure to the BSE agent: infective dose and species barrier. Brussels: European Commission, 2000.

EC00c European Commission. Scientific steering committee. Summary account of a working group meeting 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. Brussels: European Commission, 2000.

EC00d European Commission. Communication from the commission on the precautionary principle. Brussels: European Commission, 2000.

Esm93 Esmonde TFG, Will RG, Slattery JM, *et al.* Creutzfeldt-Jakob disease and blood transfusion. Lancet 1993; 341: 205-7.

FDA98 Anonymous. Special report: FDA panel recommends deferral of some donors who have lived in the UK, as nvCJD precaution. ABC Newsletter 1998; (December): 18-25.

Fis00 Fischer MB, Roeckl C, Parizek P, *et al.* Binding of disease-associated prion protein to plasminogen. Nature 2000; 408: 479-83.

Fra70 Fraser H, Dickinson AG. Pathogenesis of scrapie in the mouse: the role of the spleen. Nature 1970; 226: 462-3.

Gha98 Ghani AC, Ferguson NM, Donnelly CA, *et al.* Estimation of the number of people incubating variant CJD. Lancet 1998; 352: 1353-4.

Gha00 Ghani AC, Ferguson NM, Donnelly CA, *et al.* Predicted vCJD mortality in Great Britain. Modelling the latest data puts a ceiling on the likely number of vCJD cases. Nature 2000; 406: 583-4.

GR96 Gezondheidsraad: Commissie Prionziekten. Prionziekten. Rijswijk: Gezondheidsraad, 1996; publicatie nr 1996/25.

GR00 Gezondheidsraad: Commissie Variant Creutzfeldt-Jakob ziekte en leucodepletie. Leucodepletie van bloedproducten. Den Haag: Gezondheidsraad, 2000; publicatie nr 2000/04.

Hey94 Heye N, Hensen S, Müller N. Creutzfeldt-Jakob disease and blood transfusion. Lancet 1994; 343: 298-9.

Hil97a Hill AF, Desbruslais M, Joiner S, *et al.* The same prion strain causes vCJD and BSE. Nature 1997; 389: 448-50.

Hil97b Hill AF, Zeidler M, Ironside J, *et al.* Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. Lancet 1997; 349: 99-100.

Hil98 Hilton DA, Fathers E, Edwards P, *et al.* Prion immunoreactivity in appendix before clinical onset of variant Creutzfeldt-Jakob disease. Lancet 1998; 352: 703-4.

Hil99 Hill AF, Butterworth RJ, Joiner S, *et al.* Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. Lancet 1999: 353: 183-9.

Hou00 Houston F, Foster JD, Chong A, *et al.* Transmission of BSE by blood transfusion in sheep. Lancet 2000; 356: 999-1000.

Iro00 Ironside JW, Hilton DA, Ghani A, *et al.* Retrospective study of prion-protein accumulation in tonsil and appendix tissues. Lancet 2000; 355: 1693-4.

Kit91 Kitamoto T, Muramoto T, Mohri S, *et al.* Abnormal isoform of prion protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob disease. J Virol 1991; 65: 6292-5.

Kle97 Klein MA, Frigg R, Flechsig E, *et al.* A crucial role for B cells in neuroinvasive scrapie. Nature 1997; 390: 687-90.

Kle98 Klein MA, Frigg R, Raeber AJ, *et al.* PrP expression in B lymphocytes is not required for prion neuroinvasion. Nature Med 1998; 4: 1429-33.

Kre96 Kretzschmar HA, Ironside JW, DeArmond SJ, *et al.* Diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Arch Neur 1996; 53: 913-20.

Las96a Lasmézas CI, Deslys J-P, Demaimay R, *et al.* BSE transmission to macaques. Nature 1996; 381: 743-4.

Las96b Lasmézas CI, Cesbron J-Y, Deslys J-P, *et al.* Immune system-dependent and -independent replication of the scrapie agent. J Virol 1996; 70: 1292-5.

Lee98 Lee CA, Ironside JW, Bell JE, *et al.* Retrospective neuropathological review of prion disease in UK haemophilic patients. Tromb Haemost 1998; 80: 909-11.

Pat98 Patry D, Curry B, Easton D, *et al.* Creutzfeldt-Jakob disease (CJD) after blood product transfusion from a donor with CJD. Neurology 1998; 50: 1872-3.

Poe91 van der Poel C, Cuypers H, Reesink H, *et al.* Risk factors in hepatitis C virus-infected blood donors. Transfusion 1991; 31: 777-9.

Ray97 Raymond GJ, Hope J, Kocisko DA, *et al.* Molecular assessment of the potential transmissibilities of BSE and scrapie to humans. Nature 1997; 388: 285-8.

Sch96 Schreuder BEC, van Keulen LJM, Vromans MEW, *et al.* Preclinical test for prion diseases. Nature 1996; 381: 563.

Sch97 Schreuder BEC, Wilesmith JW, Ryan JBM, *et al.* Risk of BSE from the import of cattle from the United Kingdom into countries of the European Union. Veterinary Rec 1997; 141: 187-90.

Sch98 Schreuder BEC, van Keulen LJM, Vromans MEW, *et al.* Tonsillar biopsy and PrP^{Sc} detection in the preclinical diagnosis of scrapie. Veterinary Rec 1998; 142: 564-8.

Sch99 Schmerr MJ, Jenny AL, Bulgin MS, *et al.* Use of capillary electrophoresis and fluorescent labeled peptides to detect the abnormal prion protein in the blood of animals that are infected with a transmissible spongiform encephalopathy. J Chromatography 1999; 853: 207-14.

Sco99 Scott MR, Will R, Ironside J, *et al.* Compelling transgenetic evidence for transmission of bovine spongiform encephalopathy prions to humans. PNAS 1999; 96: 15137-42.

Sul97 Sullivan MT, Schoberger LB, Kessler D, *et al.* Creutzfeldt-Jakob disease (CJD) investigational lookback study. Transfusion 1997; 37: S2.

Tay00 Taylor DM, Fernie K, Reichl HE, *et al.* Infectivity in the blood of mice with a BSE-derived agent. J Hosp Inf 2000; 46: 78-9.

Ver98 Verdrager J. New variant Creutzfeldt-Jakob disease and bovine pituitary growth hormone. Lancet 1998; 351: 112-3.

War98 Warden J, Brooks A. Surgical specimens to be tested for new variant CJD. Br Med J 1998; 317: 617.

Wil96 Will RG, Ironside JW, Zeidler M, *et al.* A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996; 347: 921-5.

Wil98 Williams N. Britain hunts down CJD epidemic in removed appendices. Science 1998; 281: 1422-3.

Wil00 Will RG, Zeidler M, Stewart GE, *et al.* Diagnosis of new variant Creutzfeldt-Jakob disease. Ann Neurol 2000; 47: 575-82.

A The request for advice

B The committee

Annexes

Annex **A**

The request for advice

The Minister of Public Health, Welfare and Sports wrote to the President of The Health Council on 27 August 1998 (letter reference GMV/MHB 984171):

In 1996, the Health Council's Prion Diseases Committee issued the Prion Diseases recommendation. In this advisory document, the Committee states that it has not been demonstrated that there is an increased risk of Creutzfeldt-Jacob disease (CJD) in man as a result of blood transfusion or the use of blood products. This has still not been demonstrated. In March 1996, the British government issued the first report of a variant of this disease (nvCJD). Most victims of nvCJD have thus far been in the United Kingdom. The infectious agent in nvCJD is very similar to the pathological prion found in cattle infected with BSE (bovine spongiform encephalopathy).

To date, general scientific opinion holds that it is unlikely that nvCJD is transmitted via cellular blood products or products derived from plasma. Nonetheless, the possibility of transmission via the specified products is not ruled out. Precautionary measures have been taken in various European member states to keep the possible risk of transmission as low as possible. Precautionary measures may involve the following: avoiding using plasma or products prepared using plasma from risk countries, withdrawing all products if an individual donor has been diagnosed with nvCJD, and where possible substituting risky products with alternatives. The above-mentioned measures are consistent with the recommendations that the CPMP recently issued in its statement*. In addition to these measures, in a number of member states of the EU, white blood cells are removed from all cellular blood products via filtration (leukodepletion).

* "CPMP Position Statement on new variant CJD and Plasma-derived Medicinal Products" commissioned by the Committee for Proprietary Medicinal Products (CPMP), 25 February 1998.

The initial arguments in favour of leukodepletion were unrelated to the prevention of nvCJD. Instead, they focused on its importance in the prevention of HLA allo-immunisation, reduction of transmission of cell-related viruses and the possible negative effects of immuno-modulation. Recently there have been indications that reducing B-lymphocyte numbers via leukodepletion can prevent the possible transmission of nvCJD via cellular blood products. Products prepared from plasma are usually not contaminated with white blood cells.

In view of current developments with regard to a possible risk of transmission of nvCJD via cellular blood products or via products prepared from plasma in man, I request that you provide me with further recommendations in this matter.

I consider the following aspects to be of relevance.

- How realistic is the chance of transmission of nvCJD via cellular blood products or via products prepared from plasma? Can a reliable risk analysis be made for the Dutch situation? If transmission is indeed possible via cellular blood products or products prepared from plasma, what might be the mechanism involved?
- What (precautionary) measures can be taken if there is a realistic chance of the transmission of nvCJD via blood transfusion? What are the pros and cons of this?
- In a number of European countries, leukodepletion is being used in connection with cellular blood products, in order to decrease a possible risk of the transmission of nvCJD. How useful is this method in relation to a risk analysis? Is there a scientific basis for this method or does it merely create an illusion of safety with respect to the possible risk of transmission of nvCJD via blood transfusion?

The Minister of Public Health, Welfare and Sports,

(signed) E Borst-Eilers

Annex **B**

The committee

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