3. RISK FROM vCJD DUE TO BLOOD

3.1 Blood Donations and Blood Processing

Appendix I - "Extraction and Use of Human Blood Products" is copied from DNV's original 1999 report for information purposes and presents the information and assumptions that have been used in this study to represent the various processes involved in the collection, processing and use of human blood. In order to make the Appendix the most useful for understanding the processes involved in producing each of the plasma derivatives, the diagram showing the production process has been amended to include products omitted from the 1999 version but the Appendix has not otherwise been updated.

In the area of England and North Wales covered by the National Blood Service (NBS) during 1996/97, 1,907,000 donors donated 2,215,000 units of usable blood. A conventional whole-blood donation consists of 450 ±45 ml of blood. The average rate of blood donation, based on 2,215,000 donations among the England & Wales population of 51.8 million for 1995, is estimated as 0.043 donations per person year.

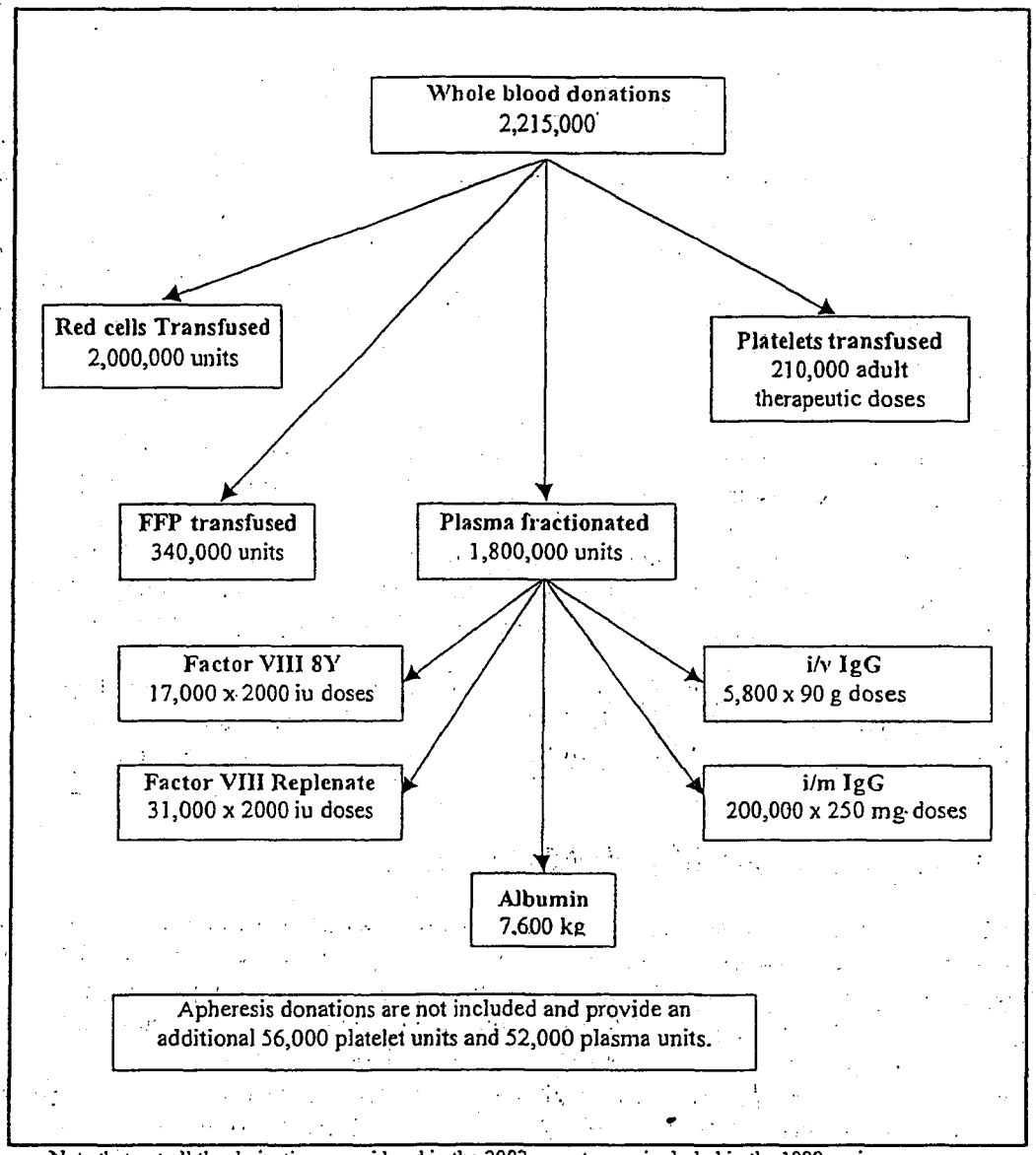
Primary processing of donated whole blood involves segregation by centrifugation into either two components (red cells + buffy coat and plasma) or three (red cells, plasma and buffy coat). The buffy coat consists of white cells and platelets. Modern medicine rarely requires whole blood transfusions and most transfusions involve one of several forms of red cells. One unit of red cells is produced from one whole blood donation. Platelets are produced from the pooled buffy coat from four whole blood donations. Until May 1998 about 80% of the collected plasma would have been sent to the Bio Products Laboratory (BPL), part of the National Blood Service, for processing into plasma fractions. The remaining plasma would be used as fresh frozen plasma (FFP) with one unit of FFP being produced from one donation.

In May 1998, BPL discontinued fractionation of UK fresh frozen plasma, in response to advice by the UK Committee on the Safety of Medicines, and now fractionates imported plasma. The data used in this report are based on 1997/98, the last full year of manufacture from UK plasma.

At BPL the plasma was typically processed in batches of about 6400 kg, containing plasma from approximately 20,000 donations. The first stage of processing plasma into blood products is cryoprecipitation followed by ethanol fractionation. This is followed by a series of stages depending on the product, involving precipitation, centrifugation, filtration, virus inactivation, formulation and heat treatment. The main plasma derivatives produced are: Factor VIII, a blood clotting agent used in the treatment of Haemophilia A and produced in two forms; Factor IX, a blood clotting agent used in the treatment of Haemophilia B; albumin, which may be transfused directly into patients and is used as an additive in formulating other medical products; and both intravenous (i/v) and intramuscular (i/m) immunoglobulin, IgG.

The main flows of these blood products in England and Wales is shown in Figure 3.1.

Figure 3.1 Products from Blood Donations in England & Wales 1996-97



Note that not all the derivatives considered in the 2003 report were included in the 1999 review.

3.2 Infectivity in Blood

Appendix II provides an overview of the available evidence for the presence of infectivity from TSEs in blood, and estimates for the level of that infectivity. All the evidence for infectivity from TSEs in blood is based on animal models. A review of epidemiological evidence concludes that there is no evidence that sporadic CJD has ever been transmitted by blood transfusion. Although such transmissions may have occurred, the numbers would have to have been very small to escape detection. However, it is not certain that this also applies to vCJD.

A number of studies have failed to show any infectivity in the blood from sporadic CJD patients when inoculated intracerebrally into monkeys, chimpanzees and guinea pigs. However, there have been 4 experiments in which infectivity was detected by intracerebral inoculation in the recipient animal (mouse, hamster or guinea pig). These results are surprising because it would be expected that it would be easier to infect primates with human CJD than rodents. There has also been criticism of these experiments in the literature (Brown, 1995). Other experiments using TSE models in laboratory animals have detected infectivity in blood when inoculated intracerebrally. There have been 4 reports of transmission following intravenous blood transfusion within the same species. These studies were on sheep with experimental BSE (Houston et al 2000) and natural scrapie (Hunter *et al* 2002), mice with a strain of human Gerstmann-Sträussler-Scheinker agent (Brown *et al* 1999) and hamsters with BSE (Rohwer 2002).

A number of experiments to estimate the level of infectivity in blood have been reviewed. These are all based on animal models and intracerebral injection and give estimates of infectivity in blood ranging from 1 to 310 i/c ID_{50}/ml. The most extensive studies by Brown and co-workers and recent work on the BSE model in hamsters (Rohwer 2002) and vCJD in mice (Cervenakova 2002) indicate levels towards the lower end of this range. Therefore, it is proposed that a value of 10 i/c ID_{50}/ml is used as the basis for this study, being at the lower end of the range (1 ID_{50} has a probability of approximately 50% of causing infection).

In order to estimate the infectivity for intravenous inoculation, it is assumed that the i/v route is 5 times less efficient than the i/c route (Brown et al 1999). Combined with the estimate of i/c infectivity above, this gives 2 i/v ID_{50}/ml blood, with a range of approximately 0 to 60 i/v ID_{50}/ml.

3.3 The Level of Infectivity in Blood Components

Brown et al investigated (as detailed in Appendix II) the distribution of infectivity in different blood components in 1998 and 1999. In 1998, they carried out two sets of experiments. The high input "spiking" experiment involved spiking hamster adapted scrapie infectivity into human blood, which was then separated by centrifugation into the three main components, red cells, white cells/platelets and plasma, and the plasma was then subjected to Cohn fractionation, as used by the American Red Cross. Titrations in each component were then determined, which showed that the majority of the infectivity went into the red cell component but that there was still significant infectivity in the plasma. However, only 32% of the infectivity in the whole blood was recovered in the three components.

In the second "endogenous" infectivity experiment (Brown et al 1998), clinically ill mice that had earlier been inoculated intracerebrally with a mouse adapted strain of human TSE were bled and the resulting 45 ml of pooled blood separated as before. Because of the need to dilute the specimens only a small fraction of each specimen was inoculated. Specimens from buffy coat, plasma, cryoprecipitate and Cohn fractions I+II+III transmitted disease to a few animals, but no transmissions occurred from whole blood, red cells or Cohn fractions IV and V. The absence of transmission from whole blood and red cells does not imply no infectivity. With the fractions inoculated, an infectivity of 10 IU/ml (1 infectious unit IU = $2ID_{50}$) in whole blood would have been expected to have resulted in less than 1 infection in the panel of 11 mice used.

A third set of experiments in which blood from symptomatic hamsters inoculated with hamster adapted scrapie was inoculated intravenously and intracerebrally into other hamsters has been reported by Rohwer in evidence to the FDA, and in presentations to conferences and expert meetings. Rohwer has also presented similar findings in mouse-adapted BSE (Rohwer 2002).

Brown et al (1999) conducted further experiments to determine infectivity of buffy coat and plasma (unfortunately, no experiments were conducted on red blood cells). The relative infectivity of the plasma and buffy coat during the symptomatic stage are very similar in both the 1998 and 1999 tests.

The results from these experiments can be interpreted in a number of ways as shown in Appendix II, Section II.3.6.6. The favoured approach is analysis of low input experiment (Brown et al 1998) with a red cell contribution of 24%, sufficient to give an overall infectivity of 10 i/c IU/ml (see Appendix II.3.5.1). The infectivity proportions are then combined with the whole blood infectivity of 2 i/v ID_{50}/ml (see section 3.2) to give infectivity values for each blood component.

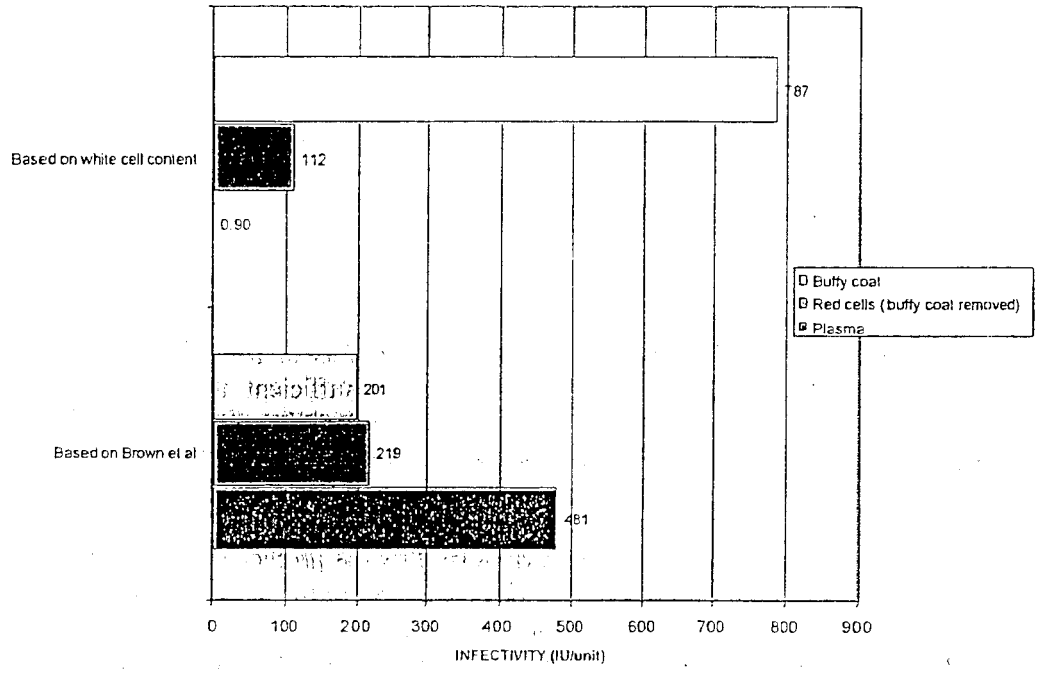
An alternative approach, based on the recent work indicating the presence of abnormal prion protein (Wadsworth *et al* 2001) or infectivity (Bruce *et al* 2001) in the lymphoreticular system of vCJD patients would be to assume that the level of infectivity would be proportional to the number of white cells present. However, the role of circulating white cells in the pathogenesis of the disease and the contribution of lymphocytes to the total infectivity in whole blood is far from clear (Raeber 2001).

Results from the two approaches are compared in Figure 3.2, which shows the infectivity per unit in red cells, plasma and buffy coat. This shows that if infectivity were related to white cell content then most of the infectivity would be in the buffy coat, a small fraction in the red cell units and very little (0.5 ID_{50}/unit) in plasma. In contrast, the Brown et al experiments indicated that about half the infectivity in whole blood was in the plasma, with the remainder being split equally between red cells and buffy coat. The studies of Rohwer on hamster-adapted scrapie and Cervenakova on mouse-adapted vCJD presented at meetings (Rohwer 2002 and Cervenakova 2002) also showed infectivity in the plasma as well as in buffy coat, although the ratios vary somewhat.

The estimates based on the interpretation of the Brown et al data described above are used in this risk assessment. This approach was favoured by all the experts and expert committees consulted.

Leucodepletion has been carried out universally in the UK since October 1999. The specification for leucodepletion is a reduction in total white cells to below $5x10^6$ white blood cells per unit of leucodepleted blood or leucodepleted platelets. This is 3 orders of magnitude lower than the number of white cells in whole blood. All subsets of white blood cells are reduced (Pennington *et al* 2001). In view of the uncertainties over the precise link between white cell content and infectivity, an infectivity reduction factor of only 2 orders of magnitude is proposed for incidents involving leucodepleted donations of red blood cells and platelets. For unfiltered platelets, reduction in infectivity is assumed to be 1 order of magnitude. No correction is made for plasma or plasma derivatives prepared from leucodepleted blood (see Appendix II.4.2).

Figure 3.2 Comparison of Estimates of Infectivity in Blood Components

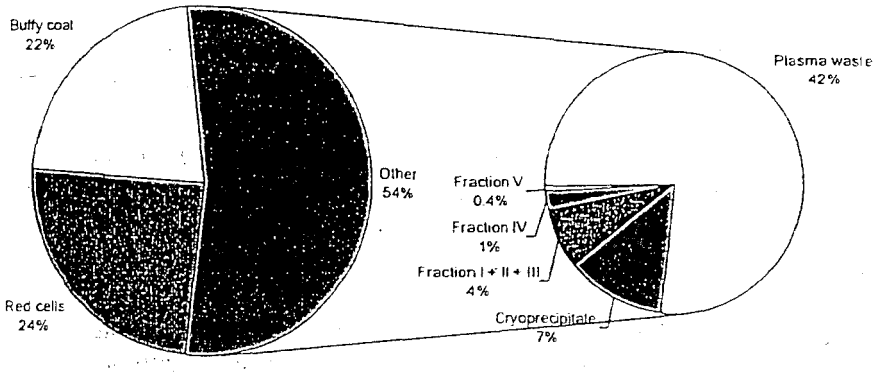


3.4 Effect of Plasma Fractionation & Blood Product Production on Infectivity

Production of the various plasma derivatives involves cryoprecipitation of the frozen plasma followed by various stages of fractionation, precipitation, centrifugation, filtration, virus inactivation, formulation and heat treatment. Several of these steps are intended to achieve a major reduction in viruses, and it is possible that they could also have a significant effect on infectivity. On the other hand, TSE infectivity has been shown to be highly resistant to conventional inactivation methods. In plasma derivative production many of the steps involve physical removal of fractions, and it is these that are expected to reduce TSE infectivity. A number of these processing steps in series, each with some affect in removing infectivity, could result in substantial reductions

The infectivity in the plasma fractions has been assessed as described in Appendix II.3.7. There are several possible ways of analysing the available data but the favoured approach is based on a combination of the Brown et al experiments 1998 and 1999. The Brown et al endogenous experiment (1998) provides data for the cryoprecipitate and Fractions I, II & III, and Brown et al 1999 experiments provide the data for Fractions IV and V (together with the relative infectivity of Fraction II in comparison to Fractions I & III). The overall proportion of infectivity in the various fractions is shown in Figure 3.3.

Figure 3.3 Breakdown of Infectivity in Blood Components and Plasma Fractions (based on Brown et al)



Three possible approaches to estimating the infectivity in the various plasma derivatives have been considered. The protein content approach (approach 3) was not considered scientifically sound by all 3 expert committees consulted and is mentioned here briefly but not considered further. The second approach is a worst case scenario.

Approach 1: Largest single clearance factor. Infectivity based on the value for plasma in the Brown et al experiments (Table II.3.12), combined with an estimate of the TSE reduction capability of the process steps, so called TSE *clearance factors (CF)*. An estimate of the potential for plasma fractionation processes to remove TSE infectivity has been made by Foster et al (1998, 1999 and 2000) based on SNBTS production methods, and the results of studies on the behaviour of brain-derived infectivity. Foster estimated both CF cumulatively and also individual CF for single process steps. Further work by Reichl et al (2002) has since indicated that clearance, although complementary is unlikely to be strictly cumulative and hence *this document considers the highest single clearance step only.* In this approach, the reduction in product volume is included in the CF, which refers to total infectivity, not infectivity concentration. It should be noted that the CF are derived from experiments based on SNBTS processes, but that the CF can be applied to BPL processes and therefore it is important to ensure that the yields of product per unit of plasma processed are comparable in order for the clearance factors to be applicable. It is worth noting that CF are usually expressed as "greater than" because of the limitations of the experiments, and actual values may be significantly higher.

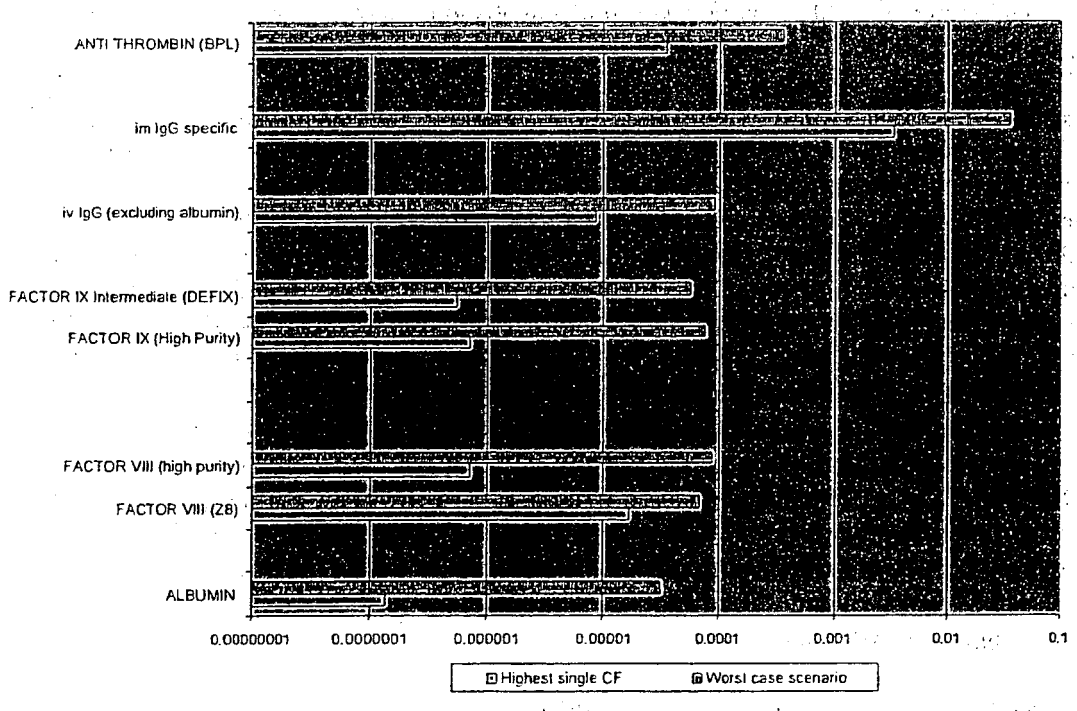
Approach 2: No additional clearance. Infectivity concentrations based on values in the Brown et al experiments (Table II.3.14) for the cryoprecipitate or other appropriate fraction, and it is assumed that there is *no further reduction* in infectivity. Hence all the load in infectivity present in the fraction is assumed to be present also in the appropriate derivative. This is a worst case, and unlikely, scenario. Further pessimism is introduced by assuming

that, where a specific fraction is used to produce more than one derivative, it is possible that all the infectivity present in the fraction can potentially end up in any one of the derivatives. This approach also requires a knowledge of the yield of each product per unit of plasma processed.

Approach 3 (considered unjustified): Protein content. Infectivity concentrations based on values in the Brown et al experiments on endogenous infectivity in the blood of animal models (Table II.3.14 of DNV report) for the cryoprecipitate or other appropriate fraction, combined with the *protein contents* in the plasma derivatives. This in effect assumes that infectivity partitions between the finished product and the waste material in proportion to the protein contents of the two. It assumes no further reduction in infectivity from further filtration steps after the fractionation (apart from that resulting from the reduction in the protein content). The scientific opinion was that it was highly unlikely that the infectivity partitions with the bulk protein and this approach was therefore unjustified.

The results from applying these first two approaches to key plasma derivatives are detailed in Appendix II.4.3 and are shown in Figure 3.4 for derivatives made from plasma batches of 20,000 donations (only 350 donations for specific immune globulins and 3,500 donations for anti-thrombin) that contain one (seven for specific immunoglobulins) from a donor who subsequently developed vCJD. The results are expressed in the form of infectivity per iu or per gram given to patients.

Figure 3.4 Comparison of Estimates of Infectivity in Plasma Derivatives (ID_{50} per iu or g)



It should be noted that at present the 2 approaches assess infectivity mainly in SNBTS products only, as they are applied to typical SNBTS product yields (BPL for Anti-thrombin). Infectivity of specific products in individual incidents will require assessment of the particular batch details, particularly if the product was not prepared by SNBTS.

Also, the CF approach estimates CF in some cases where BPL processing differs to SNBTS (see Table II.4.1 in Appendix II) based on assessment of the differences between the processes. This is because at present CF data on BPL processing is not available.

It can be seen that for Factor VIII (Z8) there is little difference in the estimated infectivity between the two approaches, whereas for most of the others the differences are substantial (e.g. about 100-fold for high purity Factor VIII).

In deciding which of the estimates to use in a particular context, factors other than scientific reasoning will need to be applied. However, the estimates may need to be revised on the basis of new scientific evidence and given the wide disparity between the current estimates, DNV considers that it is important that the assessment is updated accordingly.

3.5 Summary of Assumptions on CJD Infectivity in Blood

The following conclusions are drawn about CJD infectivity in blood:

- Blood from humans with symptomatic CJD may contain infectivity at a relatively low level. Experiments on animals indicate that it is sometimes capable of causing infection when inoculated intracerebrally into rodents. It is possible that these experiments are all flawed, but at present it is prudent to assume that blood from a person with symptomatic CJD could be infective for other humans.
- Experiments in several animals models have shown that blood from an animal infected with a TSE can be infective when inoculated intracerebrally into the same species.
- There have been 4 reports of a TSE being successfully transmitted by blood transfusion in animal models within the same species (sheep, hamster, mouse) and transmission has been shown to be possible by this means from an asymptomatic donor. No human cases are known, although a few cases could have occurred without being detected.
- Blood from vCJD cases may be infective at a higher level than blood from sporadic CJD cases, although this has not been demonstrated. This would make infection through blood transfusions more likely for vCJD.
- Evidence about the infectivity of blood from asymptomatic infections is unclear. At present, it is prudent to assume that infectivity is present throughout the incubation period.

The following assumptions are made for assessment of the infectivity of vCJD in blood:

1. Infectivity of blood from vCJD cases is assumed to be 2 human i/v ID_{50}/ml human blood (based on tests on mice with CJD). The range (based on other animal experiments) could be 0.2 to 60 human i/v ID_{50}/ml human blood.

2. Infectivity is assumed to be constant throughout the incubation period. It is also possible that it is higher at first but progressively declines through the incubation period, or alternatively that it is low at first but rises through the incubation period.

3. Infectivity in blood components is assumed to vary from the value for whole blood defined above (2 i/v ID50/ml) according to the ratios determined from the endogenous

low dose experiments (Brown et al 1998 and 1999) using blood from mice inoculated with a mouse adapted human TSE.

4. The infectivity in plasma derivatives has been estimated using two different approaches and the scientific opinion provided to DNV in discussion of a draft of this report indicated that either approach could be justified on scientific grounds.

5. The dose-response function for vCJD infectivity is assumed to be linear with no threshold. A dose of 1 ID_{50} is assumed to give a 50% chance of infection, and smaller doses give proportionately smaller chances of infection. A dose of 2 ID_{50} or more is assumed to give certain infection. The cumulative effect of repeated doses over a one year period is assumed to be additive. Continuing doses received after the first year are ignored (see Appendix II.6.2).

It may also be relevant in assessing risks in individual incidents to consider that the incubation period for vCJD derived from blood is assumed to have a median of 15 years and a 90% range of 5 to 30 years (based on cases of CJD due to human growth hormone).

3.6 Summary of Derivation of Infectivity Levels

Figure 3.5 overleaf summarises the key steps involved in the derivation of infectivity levels.

Figure 3.5 Summary of Derivation of Infectivity Levels

		Summary	Relevant Section	Selection of Infectivity
STEP 1	*Whole Blood Infectivity*	Different experiments gave a range of infectivity from 4-300 ic ID_{50}/ml. Lower end of range selected (see Section II.3.5.7).	Section II.3.5.1 to II.3.5.7	10 i/c ID_{50}/ml whole blood
STEP 2	*Conversion Intracerebral to Intravenous*	Five fold reduction factor chosen for conversion from i/c to i/v inoculation, based on experiments.	Section II.3.5.8	2 i/v ID_{50}/ml whole blood (= 900 i/v ID_{50}/unit whole blood)
STEP 3	*Blood Components Infectivity*	A 24% infection contribution from RBC is derived as detailed in section II.3.5.1. For plasma and buffy coat, the Brown et al experiments give their proportional infectivity and combining this with 24% RBC, these are then related to the 900 iv ID_{50}/ unit whole blood infectivity derived in Step 2.	Section II.3.5.1 Section II.3.6.2 to II.3.6.6	Whole Blood: 900 i/v ID_{50}/unit Plasma: 480 i/v ID_{50}/unit whole blood RBC: 219 i/v ID_{50}/unit whole blood Buffy: 201 i/v ID_{50}/unit whole blood
STEP 4	*Plasma Fractions Infectivity*	Brown's 1998 and 1999 experimental data is used to determine the proportions of the plasma fractions infectivity and this is then related to the plasma infectivity derived in Step 3.	Section II.3.7	Cryoprecip: 46 i/v ID_{50}/unit whole blood Fract 1&III: 34.4 i/v ID_{50}/unit whole blood Fraction II: 1.6 i/v ID_{50}/unit whole blood Fraction IV: 9 i/v ID_{50}/unit whole blood FractionV: 2.6 i/v ID_{50}/unit whole blood Cryosuper: 48 i/v ID_{50}/unit whole blood

The above is for non-leucodepleted blood. Any necessary adjustments for leucodepleted blood products should be made with reference to Appendix II.4.2.

4. CALCULATOR

4.1 Introduction

This section provides a simple calculator to enable the infectivity in various blood products to be estimated. This calculator is to be used by the CJD Incidents Panel in determining the advice given to patients who are known to have received blood products prepared from material including blood from a donor who went onto develop vCJD.

4.2 Blood Components

From Figure 3.2, Appendix II Section II.4.2 and Appendix II Table II.3.12, the following infectivity levels per unit whole blood can be estimated.

Table 4.1 Infectivity Levels per Unit Whole Blood

	Infectivity (iv) ID_{50}/450ml Potentially Contaminated Whole Blood Unit	Estimated Likelihood of Infection*
Whole Blood	900	100%
Plasma	480	100%
Buffy Coat	201	100%
RBC	219	100%
RBC (leucodepleted)	2	100%
Platelets (4 donations unfiltered)#	20	100%
Platelets (4 donations filtered)#	2	100%
Plasma (filtered)	480	100%

* Based on the key assumption that infectivity is present in blood

Figures for Platelets are for a therapeutic dose, which originates from the pooling of 4 separate donations (infectivities shown assume only 1 of the donations was from a patient with vCJD). Further details are provided in Appendix II.4.2. Platelet figures do not include data for the plasma present in a therapeutic platelet dose (typical platelet therapeutic dose is 300ml, comprising 297 ml plasma and 3 ml platelets). It should be noted that the plasma may also originate from up to 4 individual donations.

For most blood components, the units administered are the same as the units or fractions prepared from a single donation. Although more than one unit may be administered per transfusion and a patient may be transfused several times, it is considered unlikely that any patient would be exposed to more than one potentially infected blood component. The same argument holds for platelet infusions (4 donations are combined for a single administration).

The infectious doses received by a patient as a result of receiving a blood component from a patient incubating vCJD is therefore equivalent to the infectivity per unit in the first column of Table 4.1. Bearing in mind that 1 ID_{50} unit has a probability of approximately 50% of causing infection of a given individual and that a dose of 2 ID_{50} is regarded as resulting in certain infection, all unit doses of potentially contaminated blood components are estimated to result in infection.

4.3 Plasma Derivatives.

The infectivity levels of the various plasma derivatives per iu or gram protein are estimated in Appendix II, Table II.4.2 and are repeated below.

Table 4.2 Comparison of Estimates of Infectivity in Plasma Derivatives

Plasma Derivative	Source	Based On largest Single Clearance Factors		Based on No Clearance Beyond Initial Fractionation	
Factor VIII Z8	Cryoprecipitate	1.7×10^{-5}	ID_{50}/iu	6.6×10^{-05}	ID_{50}/iu
Factor VIII high purity	Cryoprecipitate & Fraction V	7.1×10^{-7}	ID_{50}/iu	8.9×10^{-05}	ID_{50}/iu
High purity Factor IX	Cryosupernatant	7.1×10^{-7}	ID_{50}/iu	7.5×10^{-05}	ID_{50}/iu
Factor IX (intermediate)	Cryosupernatant	5.3×10^{-7}	ID_{50}/iu	5.6×10^{-05}	ID_{50}/iu
Normal IgG– excl. albumin	Fraction II	8.4×10^{-6}	ID_{50}/g	9.1×10^{-05}	ID_{50}/g
I/m IgG* specific	Fraction II	3.4×10^{-3}	ID_{50}/g*	3.7×10^{-02}	ID_{50}/g*
Albumin 100%	Fraction V	1.4×10^{-7}	ID_{50}/g	3.1×10^{-05}	ID_{50}/g
Anti-Thrombin†	Cryosupernatant	3.4×10^{-5}	ID_{50}/iu†	3.6×10^{-04}	ID_{50}/iu†

Except for i/m specific IgG and anti-thrombin, the results are based on infectivity resulting from one plasma batch of 20,000 donations, including one from a donor who subsequently developed vCJD.

* For i/m IgG , the results are based on infectivity resulting from a plasma batch of 350 donations (50 donors), including 7 donations by a donor who subsequently developed vCJD

† For anti-thrombin, the plasma batch size is 3,500 donations, including 1 donation from a donor who subsequently developed vCJD.

As indicated by the above table, 2 different approaches to estimating the infectivity in plasma derivatives were advised by the scientific experts and committees consulted. A third approach was considered unjustified on scientific grounds and has not been pursued. The decision as to which of the two remaining estimates should be used in any particular context will depend on factors other than scientific judgement.

It should be noted that at present the 2 approaches assess infectivity mainly in SNBTS products only, as they are applied to typical SNBTS product yields (BPL for Anti-thrombin). Infectivities are based on the process yields as detailed in Appendix II, Section II.4.3.1. Infectivity of specific products in individual incidents will require assessment of the particular batch details, particularly if the product was prepared by BPL. It should also be noted that the infectivity levels calculated allowing for clearance factors are based on the assumption that yields of products obtained in the laboratory studies to determine the clearance factors are the same as the production scale yields.

The infectivity of plasma derivatives transfused to a patient will also be dependent upon the following factors:

Size of Donor Pool
Size of Dose
Number of Doses

Size of Donor Pool

Normally about 20,000 donations of plasma are combined prior to the preparation of plasma derivatives, thus diluting any single infected plasma donation. Most of the plasma derivatives are therefore calculated from a starting product containing 480 ÷ 225ml plasma ÷ 20,000 pool = $1x10^{-4}$iv ID_{50}/ml. However, for specific immune globulins (anti-D, hepatitis B, tetanus, rabies, Varicella zoster) the number of donations pooled is usually much lower and varies from less than 50 to 4,000 and may also contain more that one unit from the same donor. The risk assessment for each incident will need to be based on the characteristics of

the batches in question. In order to obtain some estimate of the possible exposure, a dilution factor 350 donations (from 50 donors) has been used for calculating the exposure that might be experienced for specific immune globulins. For Anti-thrombin, the pool size is of the order of 3,500. *These calculations are provided as illustrations. For each individual incident, the details of the batch characteristics should be used.*

Size of Dose

This is highly variable depending on the plasma derivative. Each product must therefore be considered individually. In general, however, the amounts are large compared with the traces of tissue transferred to patients from contaminated surgical tissues.

Number of Doses per year

Some patients receive repeated treatments with plasma derivatives and this assessment considers the total exposure that may occur over one year. In calculating the total potential exposure of individuals, it is assumed that a patient receives doses from the same batch. This pessimistic approach provides an *example* of the level of potential exposure. The risk for individual recipients will need to be calculated on the basis of the dose of implicated product that they have actually received over a one year period.

It is assumed, based on the linear dose-response model, that repeated doses over a one year period have an additive risk (such assumptions are not required for products administered on a single occasion). It is assumed that continuing doses received after the first year add no further risk (see Appendix II.6.2), based on a simple model developed by DNV to examine if there was any infectivity clearance due to the time period between regular doses.

Hence:

Annual cumulative potential infectivity levels transfused to patients in derivatives from plasma pools containing a donation from a variant CJD patient (ID_{50}). = $IAn\sum_{i=1}^{c} B_i$

Where:

I = Infectivity estimate in plasma derivative (ID_{50}/iu or ID_{50}/g protein). See Table 4.2. Infectivities are based on the process yields as detailed in Appendix II, Section II.4.3.1.

A = Correction factor for Pool Size. *I* is based on a pool size of 20,000 (or 350 for specific immunoglobulins, 3,500 for Anti-thrombin), and where this is the case A=1. If, for example, the pool size was only 10,000 for (eg.) albumin rather than 20,000 then:

$$A = \frac{\text{Assumed pool size (20,000)}}{\text{Actual pool size (10,000)}} = 2$$

n = Number of donations in the pool that are from donors who subsequently develop vCJD (note that an exception to this is for i/m IgG, where n must be the number of such donations divided by 7. This is because the infectivity value (*I*) for i/m specific IgG in Table 4.2 is calculated for a plasma batch of 350 donations made up from 7 donations each from 50 donors, one of whom subsequently developed vCJD; the infectivity has already been adjusted to take account of 7 donations from one vCJD donor).

B_i = Size of Dose *i* (g protein or iu). It is assumed that each individual dose is from the same pool.

c = Number of Doses (in any one year period) that a patient receives from a pool containing donations from donors who subsequently developed vCJD.

Because both the size and frequency of dose of plasma derivatives vary widely, Table 4.3 below should be viewed as informative only. It outlines possible infectivity levels transfused to patients via different derivatives. For the purposes of providing example calculations in the table, infectivity levels are based on the highest single CF. In specific incidents, the total annual dose will be derived by simply summing doses from the implicated batch of product.

Table 4.3 Possible Infectivity Levels Transferred to Patients in Derivatives from Plasma Pools Containing a Donation from a Variant CJD Patient [1]

Product	Infectivity in Blood Product (I) ID_{50}/g or ID_{50}/iu) [2]	Example Dose per Administration (B)	Example Infectivity (ID_{50})/dose	Example Number of administrations pa (c)	Example Infectivity (ID_{50})/year [5]
Albumin	1.4×10^{-7} ID_{50}/g protein	Chronic disease 225g	3.0×10^{-5}	6	1.8×10^{-4}
		Shock/intensive care 90g	1.2×10^{-5}	1	1.2×10^{-5}
Normal Immunoglobulin	8.4×10^{-6} ID_{50}/g protein	Replacement in immunodeficiency iv 42g	3.5×10^{-4}	20	7.1×10^{-3}
		Regulation in immune disorders iv 140g	1.2×10^{-3}	12	1.4×10^{-2}
		All other uses im 250mg	2.1×10^{-6}	?	?
Specific Immunoglobulin	3.4×10^{-3} ID_{50}/g protein	Anti-D (im 250mg [4])	8.4×10^{-4}	2	1.7×10^{-3}
		Hepatitis B and Tetanus (im 250mg [4])	8.4×10^{-4}	1	8.4×10^{-4}
		Rabies and V zoster (im 250mg [4])	8.4×10^{-4}	3	2.5×10^{-3}
Factor IX high purity	7.1×10^{-7} iv ID_{50}/iu	1250 iu	8.9×10^{-4}	52	4.6×10^{-2}
Factor IX [3] intermediate	5.3×10^{-7} ID_{50}/iu	1250 iu	6.7×10^{-4}	50	3.3×10^{-2}
Anti-thrombin	3.4×10^{-5} ID_{50}/iu	3000 iu	1.0×10^{-1}	6	6.1×10^{-1}
Factor VIII	Intermediate Z8: 1.7×10^{-5} ID_{50}/iu	2000 iu	3.4×10^{-2}	30	1.0
	High purity: 7.1×10^{-7} ID_{50}/iu	2000 iu	1.4×10^{-3}	30	4.3×10^{-2}

(1) Infectivity levels are based on the highest single clearance factor. Note that dosing regimes given are generally those in use before 1998, when plasma for derivatives production was sourced from the UK.

(2) Dilution by pooling is highly variable for specific immune globulins and in this table, a pool size of 350 donations has been used. A pool size of 3,500 is assumed for Anti-thrombin. For all other products, a pool size of 20,000 donations has been used to calculate infectivity. It is assumed that there is only one donation in a pool from a donor who subsequently developed vCJD, except in the case of specific immune globulins where that number is 7.

(3) The dosing regimes appear to be highly variable. Therefore the same value has been adopted for this mixture of factors as for factor IX alone.

(4) The immunoglobulin dose given is the total immunoglobulin content administered; the proportion of specific immunoglobulin present may be small but infectivity will be related to the total, not the specific, immunoglobulin.

(5) Because it is uncertain whether infectivity is present at all in the plasma of vCJD patients, all the values for infectivity in this table should be shown as ranges with the lower limit set at zero. However, to simplify the table, these lower zero limits have been omitted. Also, it should be noted that 1 ID_{50} has a 50% probability of causing infection.

Table 4.4 Comparison of the 2 Alternative Approaches of Possible Infectivity Levels transferred to patients in Derivatives from Plasma Pools containing a Donation from a Variant CJD Patient

Product	Example Dose Volume	Example Infectivity (ID_{50})/dose by Highest Single CF Approach	Example Infectivity (ID_{50})/dose under Worst Case Scenario
Albumin	Chronic disease 225g	3.0×10^{-05}	6.9×10^{-03}
	Shock/ intensive care 90g	1.2×10^{-05}	2.8×10^{-03}
Normal Immunoglobulin	Replacement in immunodeficiency iv 42g	3.5×10^{-04}	3.8×10^{-03}
	Regulation in immune disorders iv 140g	1.2×10^{-03}	1.3×10^{-02}
Specific Immunoglobulin	Anti-D, Hep B, tetanus, Rabies, V zoster (im 250mg)	8.4×10^{-04}	9.1×10^{-03}
Factor IX high purity	1250 iu	8.9×10^{-04}	9.4×10^{-02}
Factor IX[3] intermed	1250 iu	6.7×10^{-04}	7.0×10^{-02}
Anti-thrombin	3,000 iu	1.0×10^{-01}	1.1
Factor VIII intermed	2000 iu	3.4×10^{-02}	1.3×10^{-01}
Factor VIII high purity	2000 iu	1.4×10^{-03}	1.8×10^{-01}

- A pool size of 20,000 donations is used to calculate infectivity (except for specific immune globulins, where a pool size of 350 donations is used, and Anti-thrombin with an assumed pool size of 3,500). It is assumed there is only one donation in a pool from a donor who subsequently developed vCJD, except for specific immune globulins where that figure is 7 donations.
- The immunoglobulin dose given is the total immunoglobulin content administered; the proportion of specific immunoglobulin present may be small but infectivity will be related to the total, not the specific, immunoglobulin.
- Because it is uncertain whether infectivity is present at all in the plasma of vCJD patients, all the values for infectivity in this table should be shown as ranges with the lower limit set at zero. However, to simplify the table, these lower zero limits have been omitted.

Once the details of a particular batch prepared from a pool including a donation from a donor who went on the develop CJD are known, it may be helpful for the Panel to provide general advice about the dose at which concern would be triggered. This could be facilitated by the following table which indicates the dose (iu or g) of product that contains an estimated 1 ID_{50}.

Table 4.5 Estimates of the Dose of Each Product that Contains 1 ID_{50}: Comparison of Two Alternative Approaches

	Highest Single Clearance Factor	Worst Case Scenario
Albumin (g)	$7.4\times10^{+06}$	$3.3\times10^{+04}$
Factor VIII (Z8) (iu)	$5.9\times10^{+04}$	$1.5\times10^{+04}$
Factor VIII (high purity) (iu)	$1.4\times10^{+06}$	$1.1\times10^{+04}$
Factor IX (High Purity) (iu)	$1.4\times10^{+06}$	$1.3\times10^{+04}$
Factor IX Intermediate (DEFIX) (iu)	$1.9\times10^{+06}$	$1.8\times10^{+04}$
Normal IgG (excluding albumin) (g)	$1.2\times10^{+05}$	$1.1\times10^{+04}$
im IgG specific (g)	$3.0\times10^{+02}$ *	$2.7\times10^{+01}$ *
Anti Thrombin (BPL) (iu)	$2.9\times10^{+04}$	$2.8\times10^{+03}$

*It is assumed that there is only one donation in a pool from a donor who subsequently developed vCJD, except in the case of specific immune globulins where that number is 7 donations.

5. CONCLUSIONS

1. It is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge, it is not possible to draw any firm conclusion as to whether or not infectivity can be transmitted through human blood transfusions or plasma derivatives.

2. The evidence for infectivity in blood is based on experiments with animal models that have shown that blood from an animal artificially infected with a TSE (transmissible spongiform encephalopathy) can be infective when inoculated intracerebrally into the same species. There have also been 4 published reports of a TSE being successfully transmitted by blood transfusion in animal (sheep, hamster, mouse) models and these include transmissions from donors in the asymptomatic stage of disease.

3. Infectivity appears to be associated with white blood cells, but it also occurs in other components of blood, particularly the plasma.

4. If it is assumed that blood from a person infected with vCJD can carry infectivity, and the level of infectivity is as suggested by the animal models, then the infectivity level in a full unit of red blood cells, platelets or plasma (including leuco-depleted) may be sufficient to cause infection. Patients receiving any of these products from an infected donation would therefore be at risk of infection. This conclusion seems to be valid across a wide range of assumptions regarding the infectivity of blood components.

5. The infectivity levels in certain plasma derivatives could be such that recipients of these products, if derived from an infected plasma pool, would have a risk of infection. This result is highly uncertain, and varies significantly with the assumptions made about the level of infectivity and its distribution across plasma fractions. Two alternative approaches to estimating infectivity in plasma derivatives have been included in this report. Since the size of dose, number of doses and the size of the plasma pool all affect the potential risk, a "calculator" has been included in this report to make explicit the process of calculating the risk.

6. The levels of infectivity in blood components and plasma fractions have been estimated based on experiments in an animal model. The applicability of these data to vCJD infectivity in human blood is not known, but they are the best data available.

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