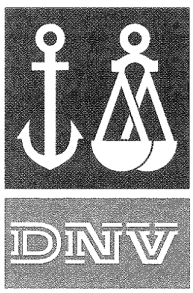
CJD/20



DET NORSKE VERITAS

DET NORSKE VERITAS

Det Norske Veritas Limited
Technical Consultancy Services

Palace House
3 Cathedral Street
London SE1 9DE
United Kingdom

Tel : +44 (0) 171 357 6080
Fax : +44 (0) 171 357 0961

Registered in England
No.: 1503799

Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products

DRAFT REPORT

For the

Spongiform Encephalopathy Advisory Committee

and the

Department of Health

CONFIDENTIAL

Approved by: GRO-C

Philip J Comer
Director of Client Services

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Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products

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Management Summary

The objectives of this study are to assess the magnitude of the risk that could result from the infective agent for vCJD being present in blood, to identify those groups of patients most at risk and to consider the effectiveness of possible measures to reduce the risks. Whilst the available evidence for infectivity in blood is reviewed, and it is concluded that blood from people with vCJD may cause infections through blood transfusions, this has not been proved conclusively, and *it is not the purpose of this assessment to provide an answer to this question.* The study is based on *the assumption* that infectivity is present in blood.

The study uses a mathematical model that tracks the way in which infectivity is transferred, initially within cattle to give rise to the BSE epidemic, then to people via food to result in vCJD cases and finally via blood transfusions and blood products to give rise to additional vCJD cases. At each stage assumptions have to be made about the factors that characterise the infectivity and the way in which the disease develops. There is considerable uncertainty about many of these factors, and hence considerable uncertainty in the predicted results. With this uncertainty, a key measure of the risk from blood will be an estimate of the percentage increase in the number of vCJD cases estimated to be due to blood rather than the absolute number itself.

Conclusions:

1. Infectivity levels appear to be such that full units of red blood cells, platelets or plasma may be able to cause infection, and so patients receiving these products are most exposed.
2. It is estimated that infectivity in blood could result in a 52% increase over the numbers of vCJD cases due to infectivity in food. This increase is dependent on the size of the food epidemic, and rises from about 10% for a small total number of cases to 80% if the total epidemic exceeds 100,000 cases.
3. The study results indicate that, if vCJD can be transmitted by blood, then the risks are significant and would justify significant risk reduction measures.
4. The estimated numbers of cases and percentage increase due to blood are not sensitive to the estimate of the level of infectivity in blood within the range of likely values.
5. With the best estimate for the level of infectivity in blood, Leucodepletion would only have a small effect on the expected numbers of vCJD cases. This conclusion is very dependent on the level of infectivity in blood and the expected effectiveness of leucodepletion in removing infectivity.
6. Infection through plasma derivatives appears unlikely to add significantly to the epidemic. Eliminating the use of UK plasma for the production of blood products will therefore have minimal effect on the numbers of vCJD cases. If the infectivity in blood is 100 times greater than that assumed, then plasma derivatives would contribute about 18% of the total.
7. As most of the risk from blood is due to transfusion of red blood cells, any reduction in the use of blood will give a reduction in the expected number of additional cases. Similarly, preventing transfusion recipients from donating blood, would prevent a further 16% increase in the number of cases. This latter measure need only be applied to recipients of blood components, not plasma derivatives.
8. All modelled risk results in this report are preliminary, very dependent on the assumptions made and subject to review.

Contents

Appendices

1. INTRODUCTION

At their meeting on the 24th October 1997 the Spongiform Encephalopathy Advisory Committee (SEAC) reviewed the safety of blood and blood products, and provided advice to Government on these matters. The Committee advised that recent research has suggested that the pathogenesis of vCJD differs from that of classical CJD and that vCJD may have more involvement of lymphoreticular tissues possible involving circulating lymphocytes. SEAC recommended that the Government should consider a precautionary policy of extending the use of leucodepleted blood and blood products as far as is practicable. SEAC also recommended that risk assessments, making assumptions of various possible incidences of vCJD, be carried out to inform decisions on any measures which may be necessary to protect recipients.

In response to this request, the Department of Health organised a meeting on the 25th November 1997 for a panel of experts to discuss the basis for a risk assessment of the possible infectivity of vCJD in blood and blood products. Following that meeting, the Department of Health contracted Det Norske Veritas (DNV) to carry out a risk assessment study. This report is an Interim Report of the work completed so far.

DNV were asked to undertake this study as experts in risk assessment who had already undertaken a number of risk assessment studies of BSE for both the Environment Agency and for MAFF.

1.1 Objectives

The objectives of the risk assessment were stated to be:

- To assess which components of blood and blood products are risk factors to human health by analysing the processes involved in blood transfusion and the preparation and use of blood products.
- To identify those groups of patients which are at high risk from blood and blood products.
- To consider the benefits and disbenefits of introducing a range of measures aimed at reducing the risks identified above.

2. OVERALL APPROACH

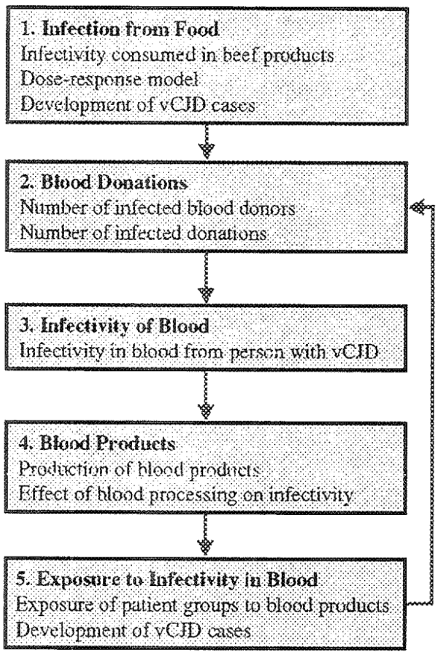
The overall approach to this risk assessment is based on that used in previous studies for the Spongiform Encephalopathy Advisory Committee, such as 'Assessment of Risk from Possible BSE Infectivity in Dorsal Root Ganglia'. A central assumption to this approach is that variant CJD is caused by consumption of the infective agent of BSE present in food derived from cattle incubating BSE, and that the risk to people of being infected by vCJD can be estimated by assessing the ingestion of BSE infectivity.

In trying to assess the risk of being infected by vCJD due to blood and blood products the key question is whether the infective agent is present in blood. Whilst the evidence for infectivity in blood is reviewed (see Appendix II) ***it is not the purpose of this assessment to provide an answer to this question***. In fact the study is based on the assumption that infectivity is present in blood.

With this in mind, the objectives of the study could be re-stated as:
On the assumption that the infective agent for vCJD is present in blood, to assess the extent of the potential exposure to vCJD infectivity, identify those groups of patients at most risk and consider the effectiveness of possible measures to reduce the risks. That is what this study attempts to do.

The main steps to achieve this are summarised in Figure 1. The main features of each of these steps are described below.

Figure 1: General Approach to Risk Model



2.1 Infection from Food

In order to estimate the potential exposure to vCJD infectivity in blood it is necessary to have an estimate of the number of people who may be incubating the disease. This is the second key question underlying this study for which there is no definitive answer. Again, it is not the purpose of this assessment to attempt to provide an estimate of the potential size of the vCJD epidemic in the UK.

In order to provide an input into this study, some previous work undertaken for SEAC to estimate the potential exposure to BSE infectivity from food has been developed further to provide an estimate of the numbers of people incubating vCJD over time. This is described in Chapter 3. It should be noted here that the resulting estimates are very dependent on the assumptions made, and it is really only possible to put a range on the values. The sensitivity of the results of this study to this range will be investigated.

2.2 Blood Donation

The next stage of the study is to consider in detail how blood is collected, processed and used. This is described in detail in Appendix I, and some of the key points summarised in Chapter 4. This is used to develop a model of the number of infected blood donations that could be expected, based on the estimated number of people incubating CJD.

2.3 Infectivity in Blood

As already stated, this assessment is based on the premise that the infective agent for vCJD may be present in the blood of a person incubating the disease. The evidence for this is presented in Appendix II. This Appendix also presents the evidence for the choice of the amount of infectivity that may be present. This is an area for which there is considerable uncertainty.

2.4 Blood Products

The various ways in which blood is processed and the products produced are summarised in Appendix I. The purpose of this is to reflect our understanding of the steps and processes involved. Many of the steps involved in producing blood products such as Factor VIII, Albumin etc, are likely to be effective in removing infectivity. However, it is hard to demonstrate this. They also involve very significant dilution. The model of infectivity in blood products takes account of the pool size from which products are made, and thus the expected number of infected donations included, and the fraction of material present in the final product.

2.5 Exposure to Infectivity in Blood

The final stage of the analysis is to assess the exposure of the population to infectivity in blood by considering the amount of blood transfused and the treatment of patients with blood products. This needs to consider the relative vulnerability of different patient groups depending on treatment regimes. The potential for patients treated with infected blood to develop vCJD will then depend on the dose received, the incubation period of the disease and also on their life expectancy. The final step would then be to close the loop and consider the new infections caused by blood affecting the donor population.

3. INFECTION FROM FOOD

3.1 Introduction

A study was carried out by DNV in October/November 1997 to assess the potential exposure of the UK population to BSE infectivity in food. This was proposed by SEAC at their meeting on the 19th September 1997 in part to put the results of the assessment of the risk from dorsal root ganglia into context. An interim report "Assessment of BSE Infectivity in Food for Human Consumption" dated 27th November was prepared and discussed at the SEAC meeting on the 2nd December. It was recognised that many of the inputs into this study were uncertain and needed to be improved before the results could be used, and it was the intention that the study would be reviewed and modified as appropriate.

Some of the work needed to develop the Assessment of BSE Infectivity in Food study has been carried out in order to provide the necessary input into this assessment. The fundamental approach is the same as that reported in the Interim Report, and the main developments included are reported here. This process is not yet complete and the report has not been reissued.

The basic approach was:

1. To review and evaluate all the potential pathways by which people could be exposed to BSE infectivity in the food chain. This included both consumption of potentially infected tissues and contamination in the abattoir.

2. To consider the infectivity density in the various bovine tissues. This included assuming a low level of infectivity (at 1% of the limit of detection) in meat. A summary of the basis for assessing infectivity in bovine tissues is given in Section 3.2.

3. To estimate the numbers of animals with a significant level of infectivity that may have been slaughtered for food. In the Interim Report this was based on the numbers of mature cattle slaughtered as opposed to prime beef before the introduction of the OTMS, and subsequently on the numbers of BSE cases in animals less than 38 months. This latter was based on the findings from the pathogenesis experiment that there was infectivity present 3 months before clinical symptoms but not 9 months before.

4. To combine the above to estimate the total numbers of infective units consumed. In doing this factors to take account of differences in consumption over time and the implementation of the SBM regulations were included.

3.2 Infectivity of Bovine Tissues

The infectivity (i.e. the potential to cause infection) of tissue from cattle with BSE is expressed in terms of its ID_{50} value. This is the dose (i.e. the quantity which each person would need to consume) to cause infection of 50% of the exposed population. This term acknowledges that some people may become infected from much smaller doses, while others may be uninfected after consuming much larger doses.

3.2.1 Infectious Dose for Cattle

Oral challenge tests on cattle are in progress at the MAFF Central Veterinary Laboratory to try and determine the minimum infective dose of BSE infected cattle brain. Some details of the present results from this "attack rate" experiment are given in Appendix II (II.5.4). As at April 1998 6 out of 10 of the animals given the minimum 1g dose have died with a mean incubation period of 4.7 years, but others are showing early clinical signs (Wilesmith, personal communication). An extension of this experiment with lower doses has now started, but the results will not be available for some years. These results indicate that the oral ID_{50} of clinically affected BSE brain for cattle is likely to somewhat less than 1 gram, although with the incubation period now being close to that observed in the epidemic it may be close to 1 gram. It was decided to take a precautionary view and assume that the mean value of the oral ID_{50} for cattle is 0.1 gram (i.e. 10 oral ID_{50} units per gram).

3.2.2 Infectious Dose for Humans

The infectivity of BSE for humans is expected to be lower than in cattle due to the species barrier. In the absence of experimental data on the cattle-human species barrier, SEAC have suggested a probabilistic uncertainty analysis using values of 10, 100, 1000 and greater than 1000 with equal probabilities, and less than 1% probability of it being 1.

In the interim Food Risk study a best-estimate value of 10 was used, being the most pessimistic of the relatively likely values suggested by SEAC. This gave a best estimate of the oral infectivity of whole-brains from BSE cases for humans of 1 human oral ID_{50}/gram, with a confidence range of 0.0001 to 10. In this update a range of values has been used.

3.2.3 Infectivity of Other Bovine Tissues

The basis for assessing the possible infectivity in other tissues is based on the limited data available from mouse bioassay experiments, with results given in terms of mouse intracerebral (i/c) units. Whilst no infectivity has been detected in an extensive list of tissues tested from clinical BSE cases, it is possible that some could exist at a level below the detection limit of the mouse bioassay. The detection limit of the mouse bioassay is taken to be 100 mouse i/c ID_{50} units per gram; this would be equivalent to an infectivity density for humans of 3.2×10^{-3} human oral ID_{50}/gram assuming that the oral infectivity of whole-brains from BSE cases for humans is 1 human oral ID_{50}/gram.

In the absence of any better data, it has been assumed that the infectivity in SBM (other than brain, spinal cord and retina) is 10% of the detectability limit, i.e. 3.2×10^{-4} human oral ID_{50}/gram. The infectivity in meat and other tissues (blood, gut content, bones etc) would be expected to be lower than in SBM, although tests on mice are unable to confirm this. In the absence of any data, it will be assumed that the infectivity per gram in these tissues is 10 times lower than estimated above for SBM, i.e. 1% of the detectability limit, and 3.2×10^{-5} human oral ID_{50}/gram.

These assumptions may be combined to estimate the total infectivity in a symptomatic BSE case. This is presented in Table 3.1.

Table 3.1 : Total Infectivity in BSE Case
(assumes that the oral infectious dose for cattle is 10 ID_{50} per gram, and that the cattle human species barrier is 10)

TISSUE	INFECTIVITY DENSITY (human oral ID_{50}/g)	MASS OF TISSUE (kg/animal)	TOTAL INFECTIVITY (human oral ID_{50}/animal)	CONTRIBUTION TO TOTAL (%)
SBM				
Brain	1.0	0.5	500	62.5
Spinal cord	1.0	0.2	200	25.0
TGG*	1.0	0.02	20	2.5
Distal ileum	0.032	0.8	25.3	3.2
Eyes	0.0016	0.1	0.2	<0.1
Other SBM	0.00032	26.8	8.5	1.1
Total SBM		28.4	754	94.2
Blood	0.000032	18.0	0.6	0.1
Carcase meat	0.000032	172	5.4	0.7
DRG*	1.0	0.03	30	3.8
Other tissues	0.000032	318.6	10.1	1.2
TOTAL		537	800	100

(*TGG = Trigeminal Ganglia, DRG = Dorsal Root Ganglia)

This assessment suggests that the total infectivity in a clinical case is 800 human oral ID_{50} units, with 94% of the infectivity in the SBM. The infectivity in the carcase meat, not including the dorsal root ganglia, is estimated to be 5 human oral ID_{50} units (0.03 ID_{50} units/kg), which is less than 1% of the total.

3.3 Updated Assessment

In updating the assessment the first two stages described above have remained effectively the same, apart from using different values for the species barrier. There still remains a need to review many of the assumptions used in assessing consumption of different tissues, but these are not expected to have a major effect on the results. The main changes that have been implemented are in improving the modelling of the BSE epidemic and the estimates of the numbers of highly infected animals slaughtered.

3.3.1 The BSE Epidemic in Cattle and Consumption of Infectivity

The starting point for this assessment is an estimate of the numbers of animals infected with BSE each year. This has been based on the results of the back calculation model reported by Ferguson et al (1997). A simple model combining the average life expectancy of cattle with an incubation period of BSE is then used to predict the number of cases, the number of infected animals eaten and the numbers with advanced infections eaten. The incubation period is modelled as a log normal distribution with a mean of 5 years and a variance of 1.6 (Anderson, 1996). An advanced infection has been defined as one 75% or more through the incubation period.

The results of the model are illustrated in Figure 3.1. This shows the input data, as the total number of new infections per year, and then the three sets of results; total infectious animals eaten, advanced infections eaten and the number of cases. The model predicts a total of

190,000 cases, 730,000 asymptomatic infected cattle slaughtered for food of which 43,500 were advanced infections.

The estimates of the advanced infections eaten are then combined with the estimates of the amounts of different bovine tissues eaten to give an estimate of the overall consumption of BSE infectivity. This is shown in Figure 3.2. This shows the relative contribution of different food types. It can be seen that brain is a dominant contribution up to 1989, when the SBM regulations first came into effect. The contribution from brain then reduces from a food source to a contaminant. The overall infectivity consumed continues to rise up to 1992, and then starts to fall as the epidemic passes its peak, and then falls rapidly with the introduction of restrictions on mechanically recovered meat and the over thirty month scheme.

3.3.2 Epidemic of vCJD due to Food

The final stage in the model is to take the estimates of infectivity consumed and to use these to predict the numbers of vCJD cases that could result. This requires assuming a dose response relationship and an incubation period for vCJD. A base case incubation period of 30 years has been assumed, with a 99% range from 5 to 80 years. The choice of incubation period is described in Appendix II, (Section II.5). The model also includes a mortality rate to take account of the chance that anyone being infected will live long enough to develop the clinical disease. In order to provide a match with the known cases of vCJD the value of the species barrier is adjusted so that the cumulative number of cases up to 1997 is equal to 23.

For the base case a match is found with a species barrier of 70. The results are shown in Figures 3.3 to 3.5. Figure 3.3 shows the match between the modelled and actual cases. Whilst this looks good, it does not demonstrate that the particular combination of incubation period and species barrier are correct. The potential variation is discussed further below. Figure 3.4 then shows the predicted numbers of new cases and fully developed cases, with Figure 3.5 showing the cumulative number of people infected, the number of live infections and the cumulative number of fully developed cases. This shows that this combination of assumptions results in an estimate of a total of about 40,000 vCJD cases.

These estimates are not intended to provide an accurate prediction of the size of the vCJD epidemic. The results are highly dependent on the assumptions made, and there is no basis for selecting one combination of incubation period distribution and species barrier as the most likely. The effect of variations in the input assumptions is shown in Figure 3.6. This shows the range of predictions as the mean value of the incubation period distribution is varied. Varying the mean value of the incubation period from 10 years to 40 years results in a range of values for the total number of cases from 340 to 120,000 with a median of 18,000 with an equivalent variation in species barrier from 17 to 10,000. The range of values for the species barrier required to match the epidemic to 23 cases up to 1997 lies within the range of values proposed by SEAC.

Figure 3.1 BSE Cases Predicted from Estimated Infections

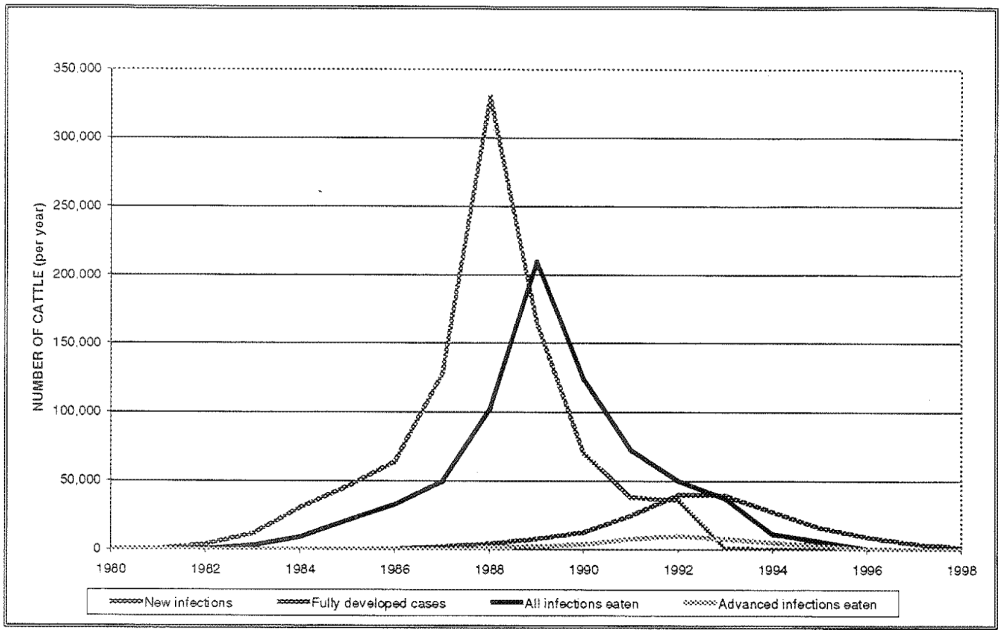


Figure 3.2 Infectivity Consumed in Food

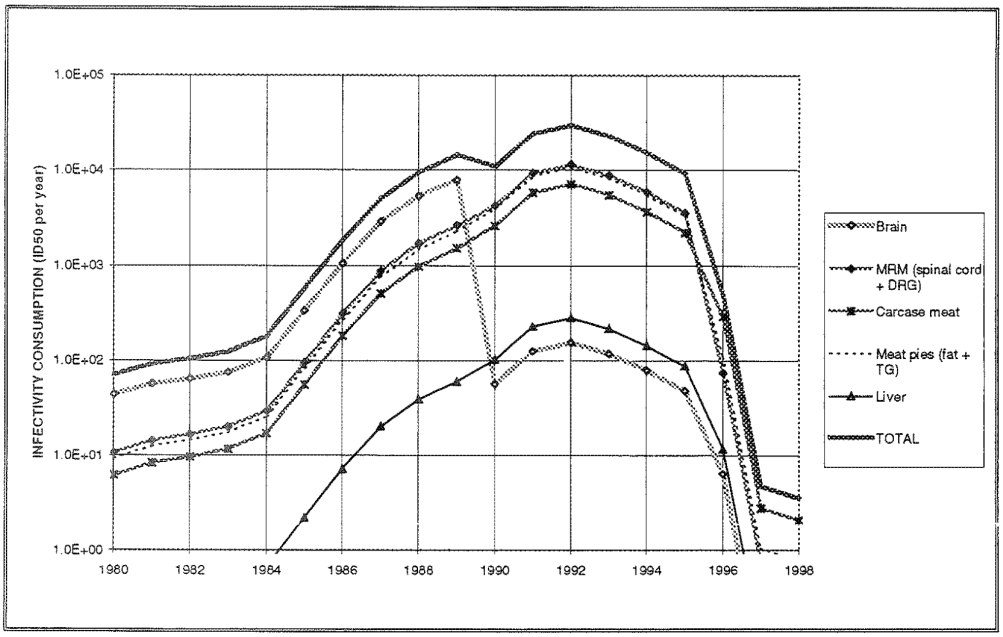


Figure 3.3 Comparison of Modelled with Actual Cases

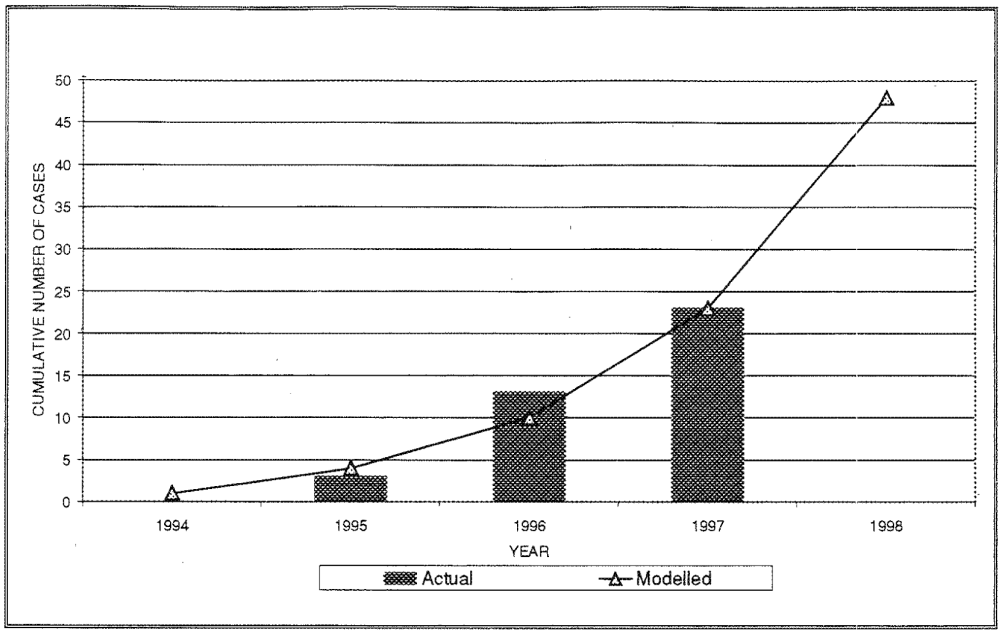


Figure 3.4 Predicted vCJD Infections and Cases (Base Case)

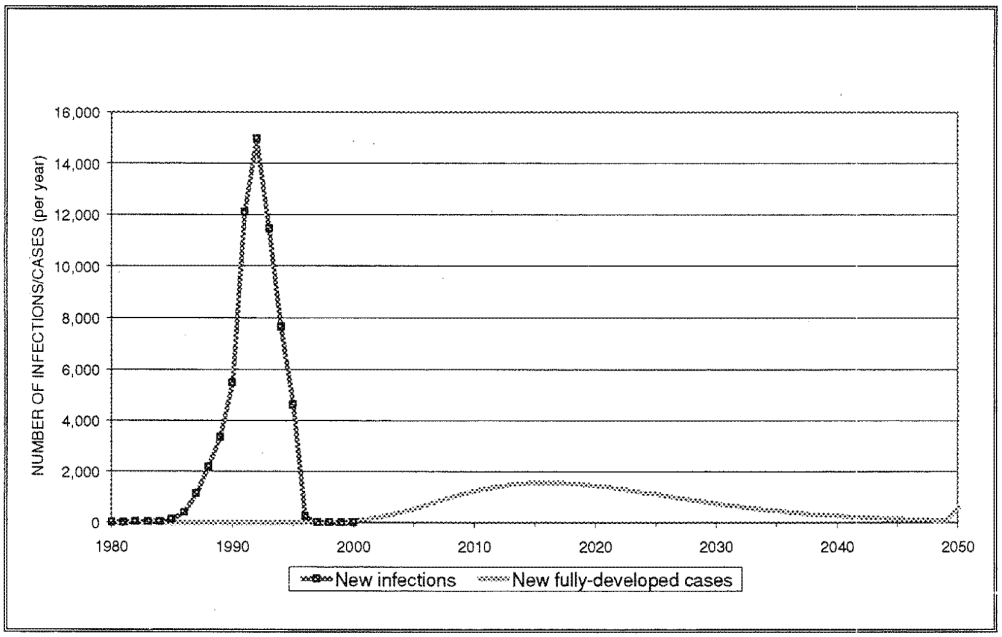


Figure 3.5 Cumulative Infections and Cases (Base Case)

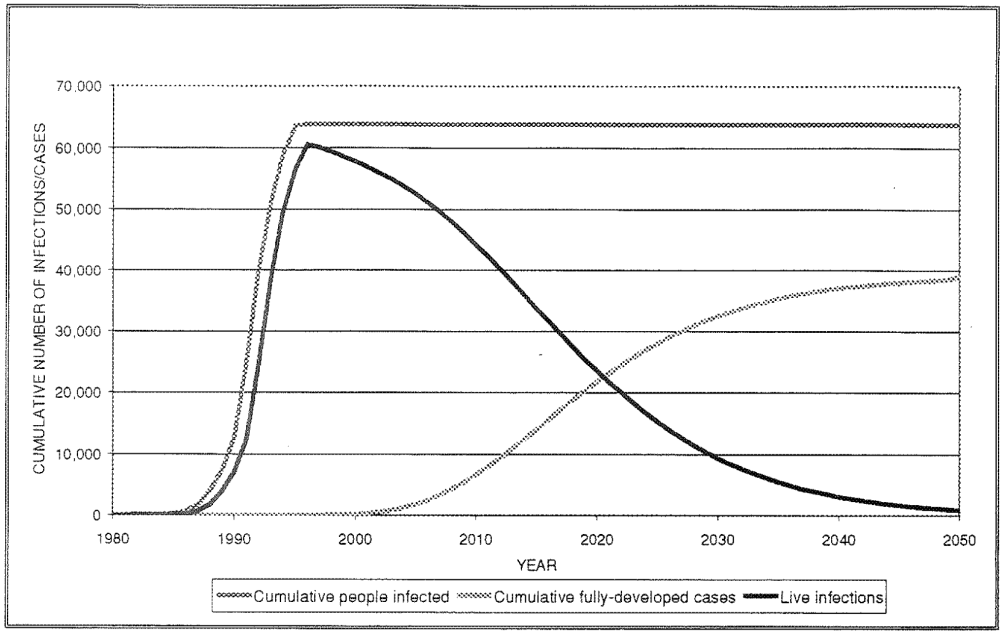
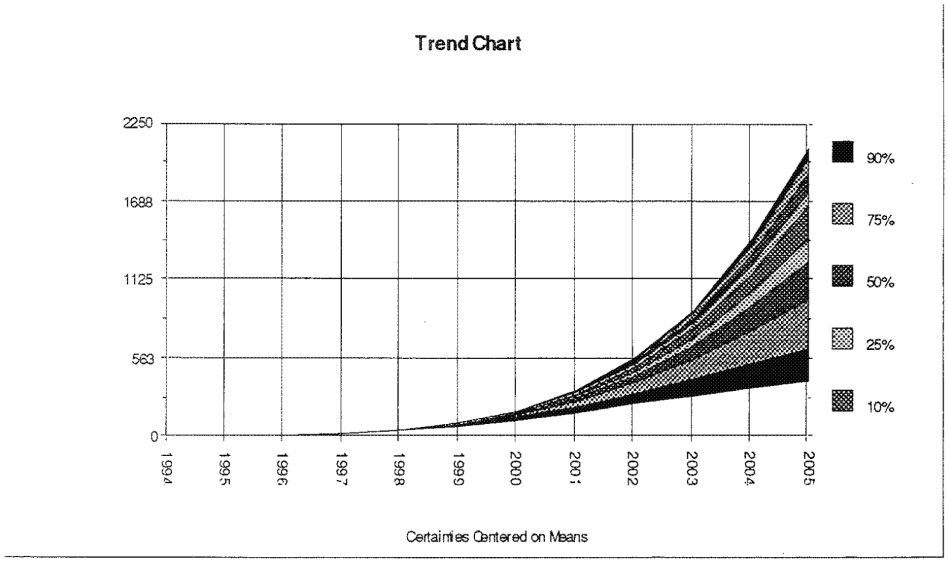


Figure 3.6 Uncertainty in Annual Numbers of Cases



4. RISK FROM VCJD DUE TO BLOOD

The model described in Section 3 enables a prediction to be made of the numbers of people incubating vCJD for a given set of assumptions on the consumption of infectivity in meat, the incubation period for vCJD due to exposure to BSE infectivity in food and the cattle to man species barrier. These predictions may now be used as the input to a model to track infectivity from people donating blood who have been infected and to assess the exposure of the population to this infectivity both from blood transfusions and from blood products. As it has been shown that the number of people infected can vary widely, a key measure of the risk from blood will be an estimate of the percentage increase in the number of vCJD cases estimated to be due to blood rather than the absolute number itself.

4.1 Blood Donations and Blood Processing

Appendix I - "Extraction and Use of Human Blood Products" 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 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.

4.2 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 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.

A number of experiments to estimate the level of infectivity in blood have been reviewed. They give estimates of infectivity in blood ranging from 0.2 to 100 i/v ID_{50}/ml. For the present study, it is proposed that the value of 1 i/v ID_{50}/ml should be used.

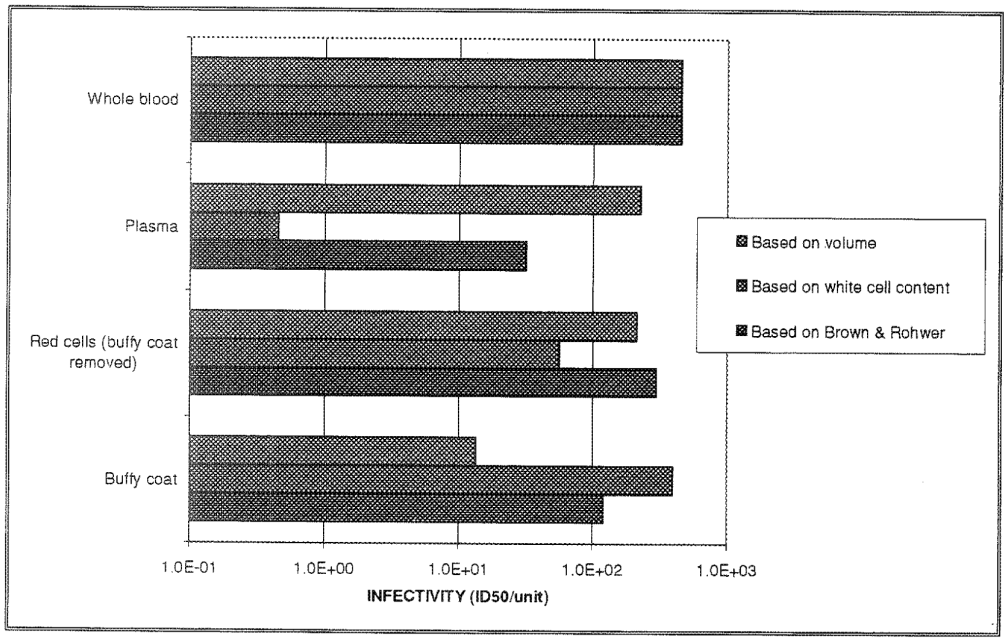
4.3 The Level of Infectivity in Blood Components

The only known investigation of the distribution of infectivity in different blood components is that of Brown & Rohwer (1998). This involved spiking hamster adapted scrapie infectivity into human blood, which was then separated by centrifugation into red cells, white cells/platelets and plasma components, and the plasma was 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 white cell/platelet component but that there was still significant infectivity in the plasma.

An alternative approach, based on the recent work implicating B lymphocytes in the development of experimental scrapie, would be to assume that the level of infectivity would be proportional to the number of B cells present. There is no data on the numbers of B cells in each blood product, so these are assumed to be in proportion to the number of white cells.

Results from the two approaches are compared in Figure 4.1, together with estimates based on component volume. The results have been expressed as ID_{50} units per unit, adjusted to give an infectivity of 1 ID_{50}/ml (450 ID_{50}/unit) of whole blood.

Figure 4.1 Comparison of Estimates of Infectivity (ID_{50}/unit)



The approach based on experiments by Brown & Rohwer lies between the two other approaches for plasma and buffy coat, but is more pessimistic for red cells. Although many aspects of the work are questionable and uncertain, it does provide a reasonable estimate of the infectivity levels. It also has the advantage of giving the infectivity level in the plasma fractions.

4.4 The Effect of Blood Processing on Infectivity

4.4.1 Component Segregation and Leucodepletion

Primary processing of donated whole blood involves segregation into the main components (red cells, plasma and sometimes platelets) by centrifugation. The infectivity in these components is shown in Figure 4.1. Leucodepletion involves removal of white cells from the blood by simple filtering. This is believed to reduce the white cells by 3 orders of magnitude. An optimistic estimate would be that it had the same effect on the infectivity. However, it is possible that some fragments of white cells may pass through the filter. This is particularly likely if filtering is done at a late stage. A more plausible pessimistic model might be to assume that leucodepletion reduces the infectivity by 2 orders of magnitude.

4.4.2 Plasma Fractionation and Blood Product Production

Some 85% of the plasma collected by the NBS is sent for fractionation at BPL. The blood is processed in batches of about 6400 kg, containing plasma from approximately 22,000 donations. The first stage of processing plasma into blood products is ethanol fractionation. This is followed by a series of stages depending on the product, involving 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. A number of these processing steps in series, each with some affect in removing infectivity, could result in very substantial reductions. For example Albumin has 9 or 10 steps each of which could reduce infectivity. On the other hand, since conventional virus inactivation methods have little effect on TSE infectivity, this could be the case in plasma derivative production as well.

The base case approach adopted for this study is to take the infectivity density based on Brown & Rohwer's spiking experiment (Appendix II, Table II.3.8) for the appropriate fraction. This reflects the reduction in mass in the final product, and assumes no further reduction in infectivity from the further processing steps. For example, Factor VIII is produced from cryoprecipitate, which is estimated to have an infectivity density 1.05 logs less than whole blood, i.e. $10^{-1.05}$ ID_{50}/ml x the fraction of donations infected. A typical 2000 iu dose is assumed to contain 0.48 g of protein. Hence the infectivity would be 4.3×10^{-2} ID_{50} per 2000 iu dose x the number of infected donations in the batch.

Estimates of infectivity for various blood products are given in Table 4.1 using this constant infectivity density approach, and compared with the estimates based on clearance factors.

Table 4.1 Comparison of Estimates of Infectivity in Plasma Derivatives Made Entirely from Infected Blood (ID_{50}/unit dose)

PLASMA DERIVATIVE AND UNIT SIZE	BASED ON CLEARANCE FACTORS	BASED ON CONSTANT INFECTIVITY DENSITY
Albumin 4.5% (500 ml)	6.4E-15	4.5E-04
Albumin 20% (100 ml)	5.7E-15	4.5E-04
Factor VIII (2000 iu)	1.2E-05	4.3E-02
Factor IX (1250 iu)	4.9E-09	3.6E-04
NHIG (250 mg)	5.7E-09	2.2E-02
Tetanus IgG (250 iu)	7.9E-05	8.9E-05
Anti D (500 iu)	6.3E-06	8.9E-05

The results in Table 4.1 show the very low infectivity estimated for all derivatives even assuming that they are produced entirely from infected blood. There are large differences between the approaches in some cases, and this indicates the very large degree of uncertainty in this part of the analysis. It is very likely that many of the process stages would have some effect on the infectivity, and thus it would be expected that the infectivity would be less than that estimated by assuming a constant infectivity density, even if it was not as low as suggested by the sum of the clearance factors.

4.5 Conclusions on CJD Infectivity in Blood

The following conclusions are drawn about CJD in blood:

- Blood from humans with symptomatic CJD appears to be infective at a relatively low level. Experiments on animals indicate that it is sometimes capable of causing infection, especially when inoculated intracerebrally into rodents. It is possible that these experiments are all flawed, but at present it is prudent to assume that human blood is infective for other humans.

- There is no evidence that CJD has ever been transmitted by blood transfusion. All such experiments in animals have failed. 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 quantitative modelling of the infectivity of vCJD in blood:

1. Infectivity of blood from vCJD cases is estimated to be 1 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 100 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. 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). For vCJD derived from BSE via food, it is assumed to have a median of 30 years and a range of 5 to 80 years (based on judgement).

4. Infectivity in blood components is assumed to vary from the value for whole blood according to the ratios determined from experiments using human blood spiked with scrapie.

5. The infectivity density in plasma derivatives is assumed to be the same as in the plasma fraction from which they are made. For a sensitivity test, the total infectivity is assumed to be reduced according to clearance factors established for each of the process steps.

6. Leucodepletion soon after donation is assumed to reduce the infectivity by 2 orders of magnitude compared to red cells with buffy coat removed (based mainly on judgement). For a sensitivity test, a reduction of 3 orders of magnitude is used (based on white cell content).

4.6 Numbers of Patients & Patient Groups

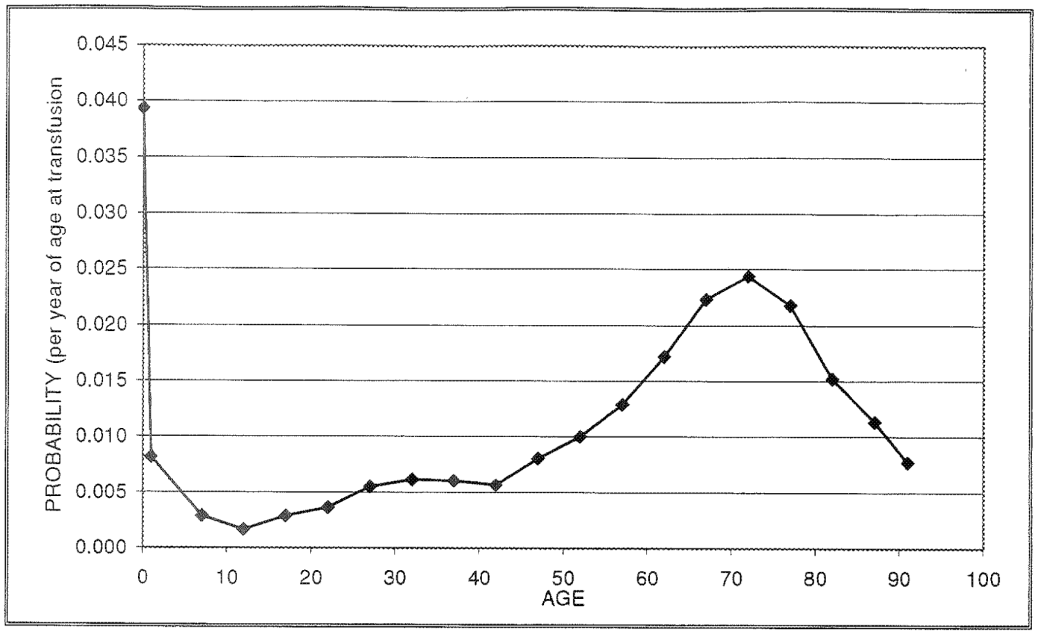
Data on the numbers of units transfused are given in Appendix I.6. The estimates of blood components transfused in England & Wales are summarised in Table 4.2.

Table 4.2 Summary of Transfused Components

COMPONENT	UNITS TRANSFUSED (per year)	UNITS TRANSFUSED (per patient)	PATIENTS TRANSFUSED (per year)
Red cells/ whole blood	2,000,000	5	400,000
Platelets	210,000	3	70,000
Plasma (FFP)	340,000	3	114,000

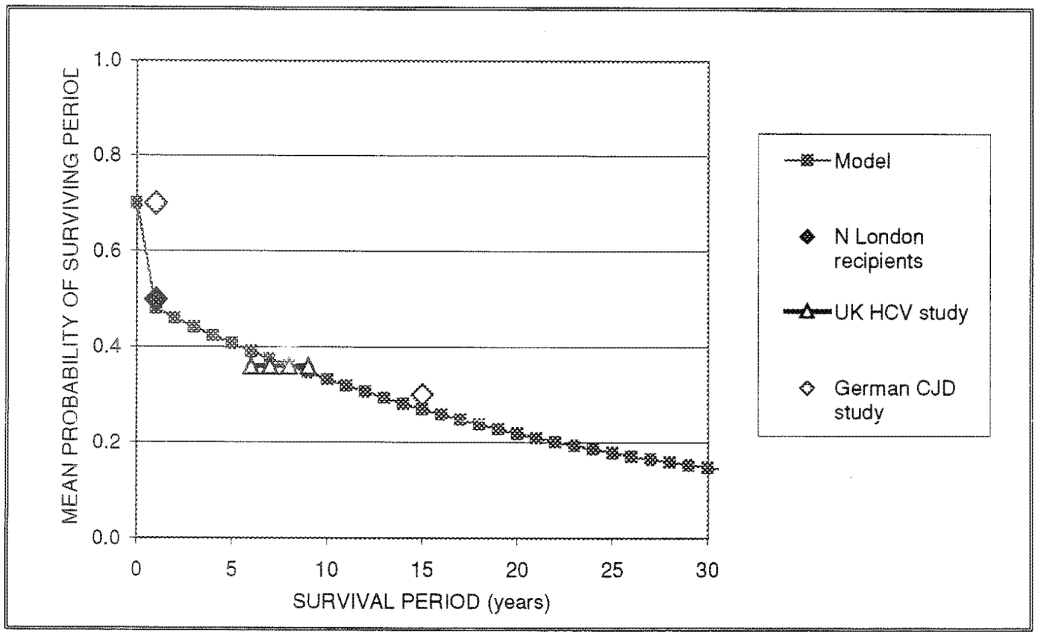
The age distribution of patients and their survival probability are important factors in estimating the number of cases of vCJD that could result given infection. The age distribution of transfusion patients in the SNBTS data is shown in Figure 4.2. It shows a narrow peak at birth, but overall most transfusion patients are aged 60-85. The distributions for all blood components are similar.

Figure 4.2 Age Distribution of SNBTS Transfusion Patents



Information on the expected survival probabilities following a blood transfusion is given in Appendix I. 6.10. For the present study, it is assumed that overall 50% of transfusion patients die within 1 year from the condition requiring the transfusion, and that patients who survive this period have largely unaffected natural life expectancy. The survival probabilities resulting from this assumption are shown in Figure 4.3, showing reasonable agreement with the data given in Appendix I..

Figure 4.3 Estimated Survival Probabilities for Transfusion Patients



In order to estimate the risks from infectivity in blood it is necessary to consider how the blood products are used to treat patients. Some patients may be treated with several different blood products. A representative set of patient groups has been developed to represent the range of treatment regimes. The treatment of individual patients varies widely, and no data has been identified that categorises the treatments systematically. Hence, the patient groups proposed are inevitably simplified and arbitrary. The numbers of patients in each group have been adjusted to match the total amounts of blood products estimated to be transfused each year.

Details of these patient groups are given in Appendix I, Section I.7. Summary information on the selected patient groups and their exposure to the major blood components is given in Table 4.3.

Table 4.3 Exposure of Patient Groups to Blood Components

PATIENT GROUP	PATIENTS (per year)	NEXT YEAR	BLOOD PRODUCT	DOSE (units/year)	LIFE EXPECTANCY (years) or SURVIVAL PROBABILITY
Acute blood loss	72,000	New	Red cells	2	90% survival
Acute blood loss + DIC	80,000	New	Red cells Plasma	5 2	50% survival
Massive blood transfusion	8,000	New	Red cells Platelets Plasma	15 3 5	20% survival
Leukaemia	42,000	Ongoing	Red cells	5	25
Leukaemia + Thrombocytopenia	63,000	New	Red cells Platelets	10 3	15
Leukaemia + DIC	28,000	New	Red cells Plasma	10 5	5
Thalassaemia	7,000	Ongoing	Red cells	5	25
Anaemia of prematurity	6,000	New	Red cells	1	50% survival
HDN babies	920	New	Red cells	1	95% survival
Other blood disorders	94,000	Ongoing	Red cells	2	15

These figures indicate a total of approximately 170,000 new patients per year, and 230,000 patients receiving on-going treatment. The former group would be eligible to donate blood in the future, and may be compared with an estimate that 6% of blood donors are aware of receiving previous blood transfusions. If donors had been exposed to the risk of transfusion for an average of 15 years, this would give a total of 2.5 million potential donors who had received one-off blood transfusions, which is 5% of the population. This is broadly consistent with the above estimate from donor recollections.

A simplified summary of the estimated exposure of UK patients to plasma derivatives made from UK plasma at BPL, prior to the changes announced in 1998, is given in Table 4.4. The BPL products are used as the basis for the present risk estimates.

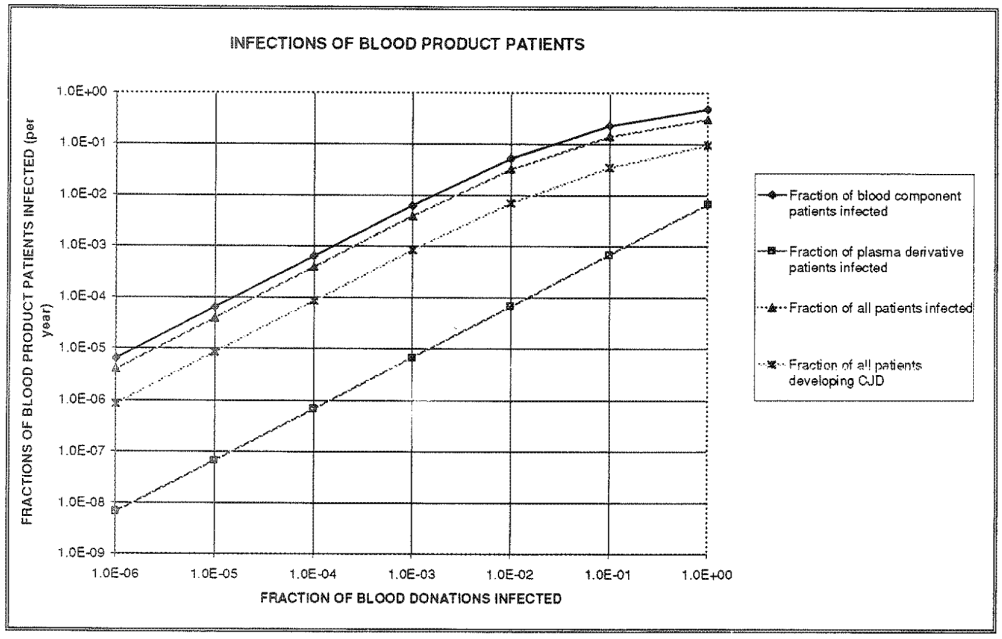
Table 4.4 Exposure of Patient Groups to UK Plasma Derivatives

PRODUCT	REPRESENTATIVE PATIENT GROUP	BPL % MARKET SHARE	BPL ISSUES (per year)	BPL PATIENTS (per year)	TYPICAL DOSE	DOSE RATE (dose/year)
Factor VIII	Haemophilia A	60	103 m iu	1800	2000 iu	27
Factor IX	Haemophilia B	60	16 m iu	250	1250 iu	52
Anti Thrombin	Sepsis	90	1.2 m iu	34	7000 iu	5
Factor VII	Warfarin overdose	70	0.75 m iu	30	4000 iu	6
Factor XI	Factor XI deficiency	100	0.13 m iu	40	1000 iu	3
Factor XIII	Factor XIII deficiency	50	0.32 m iu	6	4000 iu	12
Albumin 4.5%	Shock	90	120,000 l	59,000	1 litre	2
Albumin 20%	Intensive care	90	11,000 l	27,500	100 ml	4
i/v IgG	ITP	20	280,000 g	520	90 g	6
NIgG (i/m)	HAV prophylaxis	20	110,000 x 250mg	90,000	250 mg	1
Anti D IgG	HDN prophylaxis	75	100,000 x 500iu	67,000	500 iu	1.5
Tetanus IgG	Tetanus prophylaxis	80	8000 x 250 iu	8,000	250 iu	1
Hepatitis B IgG	HBV prophylaxis	100	3000 x 500 iu	3000	500 iu	1
Var zoster IgG	Var zoster prophylaxis	100	5400 x 250 mg	1800	750 mg	1
Rabies IgG	Rabies prophylaxis	100	530 x 500 iu	178	1500 iu	1

4.7 Risk of Infection by Patient Group

The first stage of the risk calculation is to assess the risk of infection for each of the patient groups as a function of the fraction of donations infected. This is done by combining the estimates of the infectivity per dose with the numbers of doses received by each patient group, and taking account of the life expectancy of patients in the different groups. The summary results for blood component patients and plasma derivative patients are plotted in Figure 4.4.

Figure 4.4 Fraction of Patients Infected



The plot shows that the fraction of patients infected and the fraction of patients developing CJD is directly proportional to the fraction of donations infected when this is less than about 1 in a 1000. From Figure 4.5 it can be seen that this is always true for the base case. It is estimated that there are 1.2 new infections and 0.25 new vCJD cases for each infected donation.

Figure 4.4 also shows that the fraction of plasma derivative patients infected is always about 3 logs below the fraction of blood component patients infected. In fact 99.9% of new infections and 99.7% of cases due to blood are due to blood components rather than plasma derivatives. This is because with 1 i/v ID_{50}/ml of whole blood there are about 370 ID_{50} units for an average red cell treatment. At this level of infectivity an infected dose is almost certain to produce a new infection in the recipient. With plasma derivatives the infectivity level is much less, even with a relatively high proportion of infected donations.

The numbers of infections and cases for each of the patient groups is summarised in Table 4.5, for 1 in 1000 donations from people infected with vCJD, the peak value shown in Figure 4.5. The percentages in each patient group do not change significantly with the fraction of donations infected.

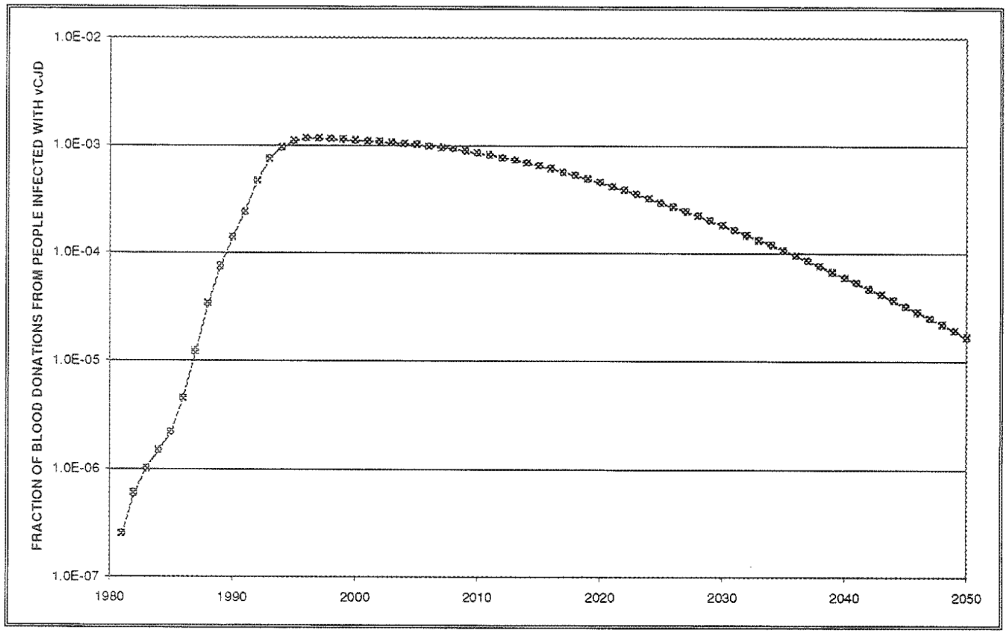
Table 4.5 Numbers of Infections and Cases by Patient Groups (with 1 in 1000 donations infected)

PATIENT GROUP	No of Infections (per year)	% Infections	No of Cases (per year)	% Cases
Blood Component Treatments				
Acute blood loss	144	5.7	65	11.9
Acute blood loss + DIC	558	22.2	140	25.6
Massive blood transfusion	182	7.2	18	3.3
Leukaemia	202	8.1	101	18.5
Leukaemia + Thrombocytopenia	793	31.6	99	18.2
Leukaemia + DIC	405	16.1	51	9.3
Thalassaemia	33	1.3	22	4.0
Anaemia of prematurity	6	0.2	2	0.4
HDN babies	1	0.04	0	0.1
Other blood disorders	185	7.4	46	8.5
Total Blood Component Treatments	2510	99.9	544	99.7
Plasma Derivative Treatments				
HDN Mothers	0	0	0	0
Shock	1	0.03	0.3	0.05
Severe Burns	0	0	0	0
Haemophilia A	1	0.04	0.8	0.15
Haemophilia B	0	0	0	0
HAV prophylaxis	1	0.04	0.8	0.14
Tetanus prophylaxis	0	0	0	0
Total Plasma Derivative Treatments	3	0.1	2	0.3
TOTAL	2,513		546	

4.8 vCJD Epidemic due to Blood

The numbers of new infections and vCJD cases due to blood can now be calculated for each year. The starting point for this calculation is the number of live infections due to food, as shown in Figure 3.6. This gives the fraction of donations infected and so the number of new infections due to blood. The fraction of infected donations by year is shown in Figure 4.5. The potential for these to develop into cases is then calculated over the incubation period distribution, taking account of the probability of surviving until the disease develops. The cumulative number of infections and cases due to blood, and the number of live infections are shown in Figure 4.6.

Figure 4.5 Fraction of Donations Infected by Year



The overall results show a total of 20,000 new cases due to blood compared to an estimated 39,000 due to food for the base case. This is an increase of 52%. The contribution of blood to the total number of vCJD cases is illustrated in Figure 4.7, which shows the cumulative number of cases due to food and to blood over the course of the epidemic. It is clear that infectivity in blood makes a significant contribution.

Figure 4.6 Cumulative Infections and Cases from Blood

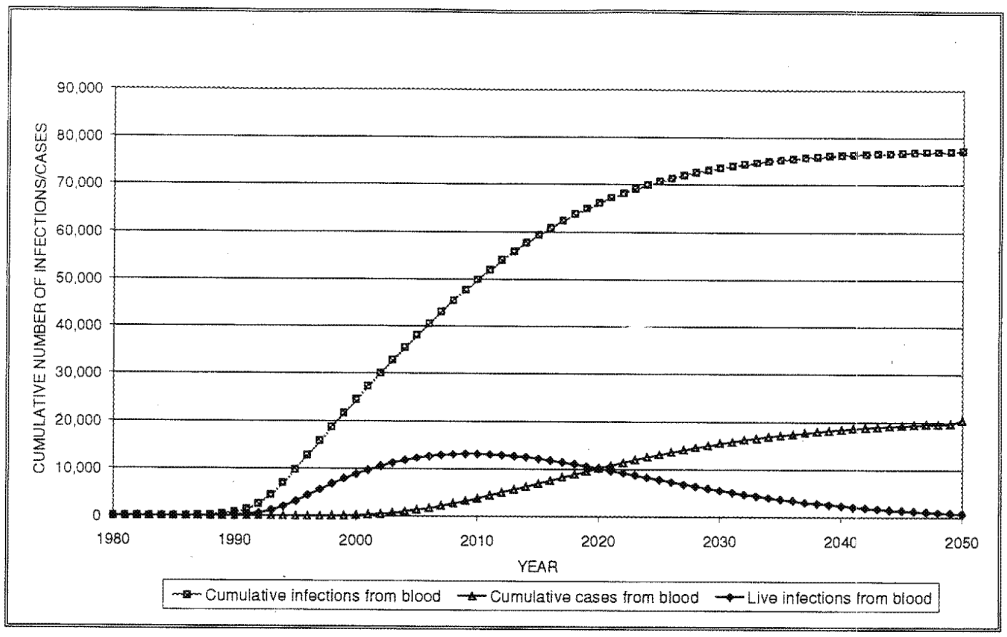
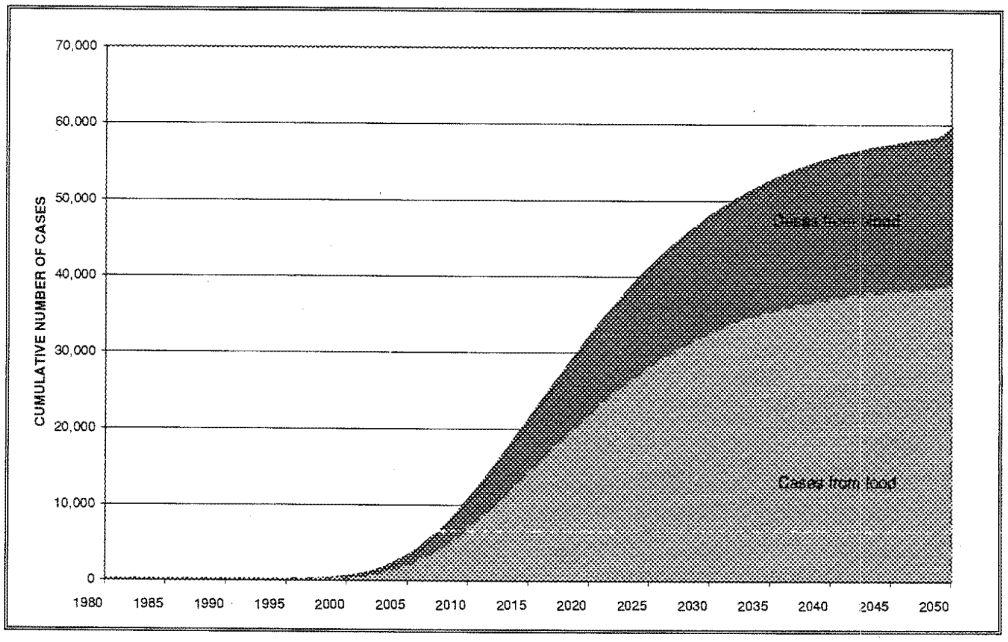


Figure 4.7 Contribution of Blood to Total vCJD Cases



4.9 Significance of the Risk Estimates

Some comparisons of the estimated risk of infection with vCJD due to blood with other sources of risk in daily life and medical procedures are given in Appendix III to help evaluate the significance of the risk estimates. In making such comparisons, it is preferable to compare the likelihood of acquiring vCJD with other diseases of similar severity. This is difficult, because of the unique and disquieting features of vCJD. Nevertheless, valid comparisons can be made with the risks of iatrogenic CJD, and to a lesser extent with the risks of sporadic CJD (although this tends to affect older people). Risks of other diseases that might be transmitted via blood such as HIV may be relevant, as well as the risks of other fatal illnesses resulting from the transfusion.

In terms of overall societal risks, the predicted peak of about 650 cases of vCJD per year due to blood transfusion is clearly much greater than the average of about 40 sporadic cases of CJD per year, but is very small compared to the 140,000 deaths from all types of cancer each year. Perhaps a better comparison is with the 430 deaths from leukaemia each year among people aged under 45.

However, public concern about vCJD due to blood products could be expected to be much greater than for leukaemia in young people, because of the very high level of uncertainty in the risk estimates. Given the absence of a scientific consensus, and the possibility that the numbers of deaths from vCJD could be very much higher or lower than estimated, public concern will naturally remain very high.

In terms of risk to an individual blood transfusion patient, the probability of infection with CJD is estimated to be 1000 times higher than the probability of HIV infection through blood products. It is estimated to be 10 times higher than all other risks of death associated with blood transfusion. It is also estimated to be only 6 times lower than the risk of CJD among children treated with human growth hormone, which was clearly unacceptable. These comparisons indicate that significant risk reduction measures are justified.

When considering whether to give a patient a blood transfusion, it is appropriate to compare the extra risks of vCJD with the benefits from the transfusion. Unfortunately, no data is available on this. However, the overall risk of death for a patient requiring a blood transfusion is estimated to be approximately 1 in 2 over the following year. Hence, the extra risk in the region of 1 in 1000 of developing vCJD may be negligible compared to the immediate benefit of the transfusion.

4.10 Sensitivity Assessment

In section 3.3.2 the effect of variations in the incubation period for vCJD due to food was investigated. It was shown that the varying the mean value of the incubation period from 10 to 40 years resulted in a range of values for the total number of cases from about 340 to 120,000 cases, with equivalent changes in the number of infections. If this range of the number of cases due to food is used as input into the blood epidemic calculation, it is found that the increase due to blood varies from about 10% with 340 total food cases, up to about 80% as the number of food cases reaches 120,000.

Another main sensitivity may be expected to be due to the infectivity in blood. However, it is found that this is not the case. This is because, as shown in Section 4.7, most of the new

infections arise from treatment by blood components, and the average infectivity per dose for treatment by red cells is 370 ID_{50} units. This results in a risk of infection of 1. Thus increasing the infectivity density of blood will have no effect on the risk of infection from blood components that represent 99.9% of the infections. Similarly, decreasing the infectivity will have no effect unless this is by more than a factor of 400. For a range of infectivity in blood of 0.2 i/v ID_{50} /ml to 100 i/v ID_{50} /ml (see section 4.2), the percentage increase in cases due to blood varies from 52% to 56%. At an infectivity of 100 i/v ID_{50} /ml the number of vCJD cases from plasma derivative treatments increases from the 2 shown in Table 4.5 to 119, 18% of the total.

5. MEASURES TO REDUCE RISK OF INFECTION FROM BLOOD

5.1 Leucodepletion

Recent work that has implicated B lymphocytes in the development of experimental scrapie, has suggested that infectivity may be contained in these cells. Also, infectivity has been found in the thyroid gland of patients with vCJD. This has led to the suggestion that leucodepletion, the removal of white cells from the blood by simple filtration, could reduce the risk of infection. As summarised in Appendix II, Section II.4.2, leucodepletion is believed to reduce the white cells by a factor of 1000 compared to red cells with buffy coat removed. An optimistic estimate would be that it had the same effect on the infectivity.

However, it is possible that some fragments of white cells may pass through the filter. This is particularly likely if filtering is done at a late stage (immediately prior to transfusion rather than soon after donation), since white cells progressively break down during this time. It is also possible in theory that filtration could release attached prion from the surface of the white cells into the leucodepleted component, although there is no evidence that this occurs. With no evidence for the reduction in infectivity due to leucodepletion it will be assumed that leucodepletion reduces the infectivity by a factor of 100. A factor of 1000 will be used as a sensitivity test.

Whilst a factor of 100 reduction would have no effect on the risk from red cells, as a dose would still have more than 2 ID_{50} units, it would reduce the risk from platelets and plasma. This is estimated to reduce the number of cases by 19%. A factor of 1000 reduction, however, is predicted to give an 85% reduction in the number of cases.

Conclusion: Unless it can be shown that leucodepletion can reduce the infectivity in blood by more than a factor of 100 it will have little benefit in reducing infectivity and only give a small reduction in the number of new cases due to blood. However, this conclusion will be sensitive to the assumptions made.

5.2 Elimination of UK Plasma Products

In January 1998 it was decided to stop using UK plasma for the production of plasma products at BPL. This followed a number of product recalls due to the identification of donations from vCJD patients in the plasma pool.

In Section 4.4.2 (and Appendix II, II.4.3) it was shown that the infectivity in plasma products derived entirely from infected donations varied from 4×10^{-2} to 9×10^{-5} ID_{50} units per dose. The maximum fraction of donations infected has been estimated to be 1×10^{-3} (see Figure 4.5). Thus the infectivity in plasma products will be less than 4×10^{-5} ID_{50} units per dose. This takes no account of the effect of the processing steps in reducing the infectivity further.

The results given in Section 4.7 show that at the peak only 2 cases (0.3%) were due to plasma products as compared with blood components.

Conclusion: Not using UK plasma for the production of plasma products will have a minimal effect on the potential numbers of vCJD cases due to infectivity in blood.

5.3 Reduction in Use of Blood Components

With the main risk of exposure to vCJD infectivity in blood coming from transfusions of red cells, and to a lesser extent platelets and plasma, any reduction in the use of blood will result in a corresponding reduction in the numbers of new cases. Clearly blood is normally only given because of need. However there are variations in the usage of blood between different hospitals, and this suggests that critical consideration of the need for blood, or the amount to be transfused, could lead to a reduction in usage. The estimated maximum probability of infection from vCJD due to a transfusion is 6×10^{-3} per patient receiving blood transfusion. This risk needs to set against the benefit that the patient would derive from the transfusion.

Conclusion: Reduction in the use of blood components will be moderately effective in helping to reduce the exposure to any infectivity in blood.

5.4 Prevention of Transfusion Recipients Giving Blood

If recipients of blood transfusions are the people most at risk from vCJD infectivity in blood, then preventing them giving blood could remove the possibility of a feed back loop that could result in further infections.

It has been estimated that about 6% of blood donors have received a transfusion in their life. The model predicts that this feedback would add a further 16% to the number of vCJD cases for the base case. This varies from an additional 3% to 23% for the range of values for the size of the epidemic.

Conclusion: Preventing recipients of blood transfusions from donating blood could result in a moderate reduction in the additional cases of vCJD due to infectivity in blood.

6. CONCLUSIONS

1. Available evidence indicates that blood from people with vCJD may cause infections through blood transfusions, although this has not been proved conclusively.

2. Infectivity appears to be linked to white blood cells, but it may also occur in other components.

3. Infectivity levels appear to be such that full units of red blood cells, platelets or plasma may be able to cause infection, and so patients receiving these products are most exposed.

4. It is estimated that infectivity in blood could result in a 52% increase over the numbers of vCJD cases due to infectivity in food. This increase is dependent on the size of the food epidemic, and rises from about 10% for a small total number of cases to 80% if the total epidemic exceeds 100,000 cases.

5. The study results indicate that, if vCJD can be transmitted by blood, then the risks are significant and would justify significant risk reduction measures

6. The estimated numbers of cases and percentage increase due to blood are not sensitive to the estimate of the level of infectivity in blood within the range of likely values.

7. With the best estimate for the level of infectivity in blood, Leucodepletion would only have a small effect on the expected numbers of vCJD cases. This conclusion is very dependent on the level of infectivity in blood and the expected effectiveness of leucodepletion in removing infectivity.

8. Infection through plasma derivatives appears unlikely to add significantly to the epidemic. Eliminating the use of UK plasma for the production of blood products will therefore have minimal effect on the numbers of vCJD cases. If the infectivity in blood is 100 times greater than that assumed, then plasma derivatives would contribute about 18% of the total.

9. As most of the risk from blood is due to transfusion of red blood cells, any reduction in the use of blood will give a reduction in the expected number of additional cases. Similarly, preventing transfusion recipients from donating blood, would prevent a further 16% increase in the number of cases. This latter measure need only be applied to recipients of blood components, not plasma derivatives.

10. All modelled risk results in this report are preliminary, very dependent on the assumptions made and subject to review.

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