II.6 Dose-Response Relationship

II.6.1 Possible Dose-Response Models

In this study, infectivity is measured in terms of ID_{50}, i.e. the dose that would cause infection of 50% of the population if administered to each. The relationship between the dose (measured in terms of multiples or fractions of ID_{50}) and the response (measured in terms of the probability of infection for an individual) is not well defined for TSEs.

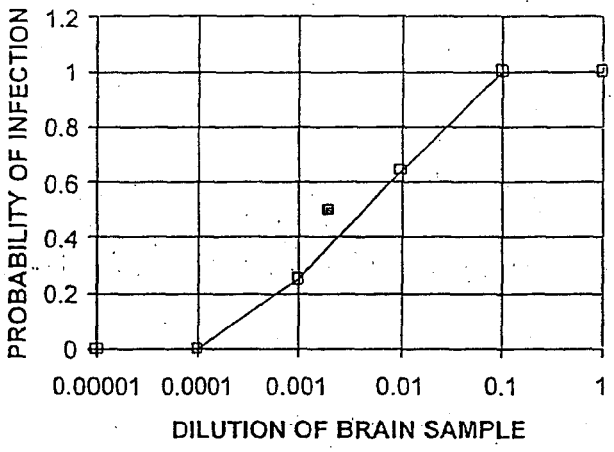
Smaller doses than the ID_{50} may cause deaths among some of the exposed population. This may be due to:

- Variation in individual susceptibility to infection.
- An element of chance in whether or not a given dose will infect a given individual.

A typical dose-response relationship is sigmoidal in shape, i.e. a plot of the probability of infection on a basis of log(dose) is S-shaped, resulting from a log-normal distribution of susceptibility in the population.

From data presented by Taylor et al (1995), a dose-response curve can be constructed for intraperitoneal injection of a relatively dilute pool of BSE infected brain into mice, as shown in Figure II.6.1.

Figure II.6.1 Dose-Response Curve for Mice Injected with BSE Infected Brain

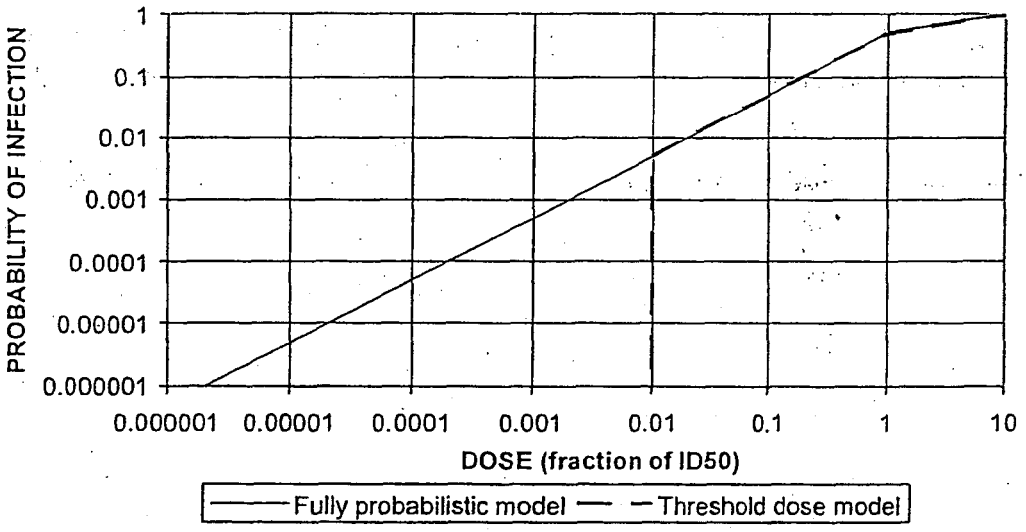


The tested populations were too small (approximately 13 mice in each group) to give precise estimates of the probabilities of infection from small doses, and the results are consistent with a more rounded sigmoid curve.

Various different forms of the dose-response relationship could be assumed for small doses. The simplest options are illustrated in Figure II.6.2:

- A linear dose-response (or fully-probabilistic) model, in which small doses have correspondingly small probabilities of infection. For example, if an ID_{50} has a probability of approximately 50% of causing infection of a given individual, a dose of 10^{-6} ID_{50} might have a probability of 0.5 x 10^{-6} of causing an infection. This linear dose-response relationship continues up to a dose of 2 ID_{50}, after which the model indicates that infection is certain. This approach will tend to overestimate the effect of small doses. This purely probabilistic dose-response model with no threshold has previously been used in quantifying risks from BSE via environmental pathways.
- A threshold dose model, assuming that small doses could exist which have no potential for causing infection. This would allow unlimited exposure to infectivity without infection, providing that the doses were always below some threshold value. This threshold model is a simple approximation to the more realistic sigmoid dose-response curve. No evidence of a threshold dose below which the probability of infection became zero was found in an analysis of 117 titration experiments in the murine scrapie model (McLean and Bostock 2000).

Figure II.6.2 Possible Dose-Response Models



- "One–hit" Poisson model, is another alternative and assumes that some minimum infectious dose (one IU) is required to transmit infection. This is a more optimistic model which assumes zero probability of infection below one IU.

II.6.2 Effect of Repeated Dosing on Infectivity

The studies of repeated dosing by Diringer et al (1998) do not give any information about the possible existence of a threshold dose, because the numbers of animals infected were too few (80 at most for any given dilution and feeding schedule). Demonstrating a threshold dose would require much larger groups of animals, preferably at dilutions of less than log steps. The rough

correspondence between log dilution and log probability of infection in fact provides evidence for the linear dose model.

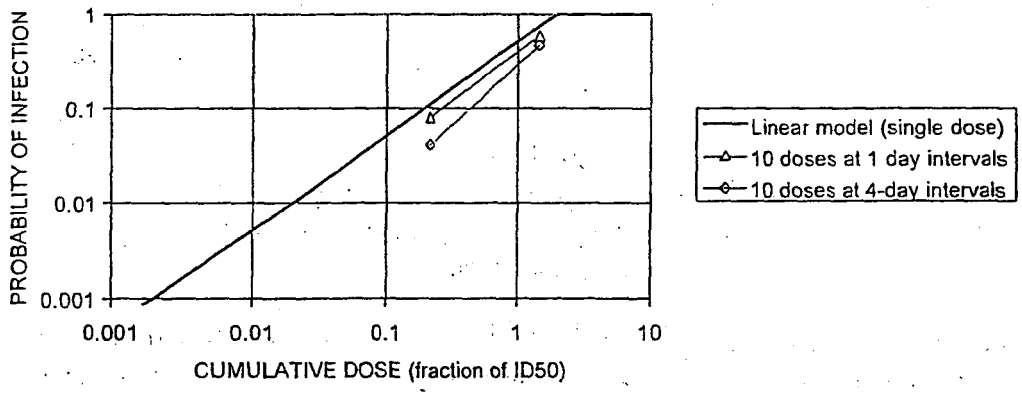
However, the studies do indicate that the dosing interval affects the probability of infection. In other words, a regular dose is less infective with longer intervals between individual doses. In addition, the cumulative effect of a regular dose is less than a single administration of the cumulative dose. If the latter effect appeared only at very low doses, it might indicate a threshold, but in fact it appears across all doses where the probability of infection is less than 100%.

This issue is important when considering recipients of plasma products, who might receive regular doses that are individually very small but cumulatively significant.

Figure II.6.3 shows the dose-response relationship implied by the results from Diringer et al (1998) for 3 feeding schedules with the same cumulative dose:

1. A single dose D (results adjusted as described by Diringer et al from a single dose of D/10)
2. 10 equal doses of D/10 at 1-day intervals
3. 10 equal doses of D/10 at 4-day intervals

Figure II.6.3 Cumulative Dose Model



A suitable practical model of these results could convert a regular dose into an equivalent single dose, with the same probability of infection. Two key issues need resolution:

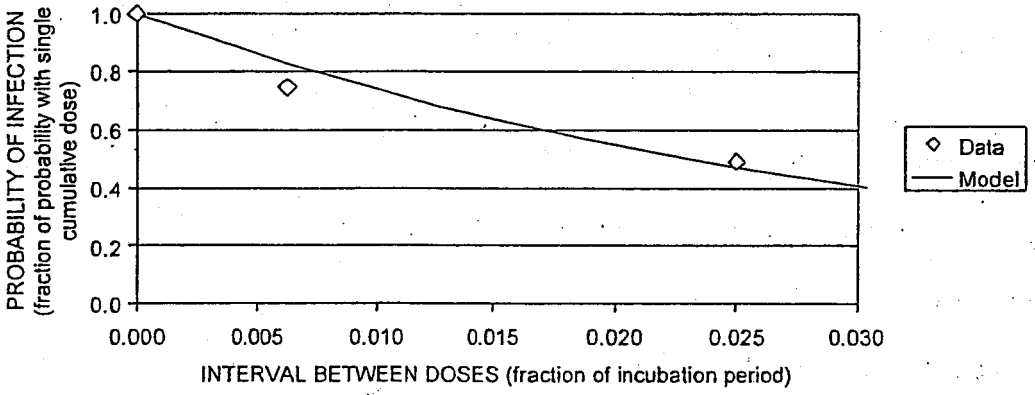
- How do 1-day and 4-day intervals for scrapie in hamsters relate to vCJD in humans?
- Over what period should a continuing regular dose be cumulated?

In the absence of any information on how to relate timescales for hamster scrapie to human vCJD, it is assumed that they scale in proportion to the incubation period of the disease. Hamster scrapie has an incubation period of about 160 days, depending on the dose (Diringer et al 1998). The median incubation period for human vCJD infection from blood is assumed to be 15 years (Section II.5.8). Hence 1 day for hamster scrapie is about 0.6% of the incubation period, and assumed equivalent to

34 days (i.e. about a month) for human vCJD. This is clearly very speculative, but is necessary to quantify the model.

Figure II.6.4 shows the average effect of dosing interval estimated from the results above. Dosing interval is expressed as a fraction of incubation period. A single dose (Schedule 1) is in effect a dosing interval of 0.

Figure II.6.4 Effect of Dose Interval for 10 Equal Doses



These results can be represented by a general model as follows:

$$D_e = D\, e^{-30\,T/I}$$

where:

D_e	=	equivalent single dose (ID50)
D	=	actual cumulative dose in time period (ID50)
T	=	mean interval between individual doses (years)
I	=	median incubation period (years)

The Diringer results only cover a course of 10 equal doses. What would be the effect of a continuing regular dose? This could be investigated by integrating the above model. A simpler approach is to neglect doses more than a year apart (in human vCJD terms), since the model shows that the effect of 10 doses a year apart is approximately 10% of the cumulative dose, i.e. roughly equal to that of the first dose on its own. This is again very speculative.

Hence the model can be expressed in terms of human vCJD as:

$$D_e = D_i\, R\, e^{-2/R}$$

where:

D_e	=	equivalent single dose (ID50)
D_i	=	individual dose (ID50)
R	=	dose rate (individual doses per year)

For example, a patient receiving a dose of 0.001 ID_{50} once per month for 20 years would have an actual cumulative dose of 0.012 ID_{50} per year, or a lifetime dose of 0.24 ID_{50}. The model above would indicate an effective dose of $0.012\ e^{-2/12} = 0.01\ ID_{50}$.

This indicates that the effect of the above model is relatively small unless the individual receives continuing doses over several years. Then its effect is to ignore doses received after the first year.

II.6.3 Proposed Approach

DNV propose to continue with the assumption that the infectivity of each individual dose follows the linear dose-relationship, with no threshold dose. This is likely to be pessimistic, although no evidence is available to improve it.

DNV developed a model (detailed in Section II.6.2) to examine if there was any clearance of infectivity due to the time period between regular doses. The model indicated that risk is not significantly reduced (relative to the large uncertainties involved in this study) except for those individuals receiving continuing doses over several years. Hence, this study assumes that the cumulative effect of repeated infective doses over a one year period will be additive, and that no further risk is accumulated after 1 year.

II.7 Conclusions

The following conclusions are drawn about CJD in blood:

- Blood from humans with symptomatic CJD appears to contain infectivity 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.
- 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.
- TSE has been successfully transmitted by blood transfusion in animal models. 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. 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 it contains infectivity 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 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 i/v ID_{50}/ml. Allowing for the possibility that blood is not infective, the range would be 0 to 60 i/v ID_{50}/ml.

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 above as shown in Table II.3.12, based on animal experiments by Brown et al (1998 and 1999).

5. The infectivity in plasma derivatives has been assessed under three different scenarios. Firstly, by assuming the derivative infectivity is reduced according to the highest single clearance factors. A worst case scenario of no infectivity clearance from processing has also been examined. A third approach considered the protein content of derivatives, but was not considered scientifically sound by all 3 expert committees consulted and is not considered further. For some derivatives there is little difference in the estimated infectivity between the two approaches, whereas for most the differences are more substantial.

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).

7. 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. DNV propose that repeated doses over a one year period have an additive risk, and that there is no increase in risk beyond one year's repeated dosing.

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APPENDIX III

SUMMARY OF ASSUMPTIONS

Contents

III. SUMMARY OF ASSUMPTIONS

III.1 Introduction

This appendix summarises the key assumptions that are used in the study.

III.2 Assumptions About Blood Infectivity

The main assumptions about blood infectivity are as follows:

1. Human blood from people incubating vCJD is assumed infective (i.e. capable of transmitting the infection to other people). The evidence is not conclusive, and it is possible that human blood is not infective in this way. It would make all risk results in this report zero, and is therefore one of the most important assumptions in the study.

2. Infectivity of blood from vCJD cases is estimated to be 10 ID_{50}/ml by intracerebral inoculation (Appendix II.3.5), based on experiments on mice with CJD. Other animal experiments give a range of 2 to 300 i/c ID_{50}/ml. Because animal experiments use particularly susceptible species and virulent disease strains, it is possible that the infectivity of blood from vCJD cases is lower.

3. The intravenous route is assumed to be 5 times less efficient than the intracerebral route (Appendix II.3.5.8).

4. 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 (Appendix II.3.4). Since the estimates of infectivity used here were based on measurements at the end of the incubation period, this could mean that the average level of infectivity during the incubation period was higher or lower than assumed here.

5. 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 - see Appendix II.5). This range represents natural variations in human vulnerability. In addition, there is uncertainty about the median value.

6. All people are assumed to be vulnerable to infection by vCJD, and genetic variations are assumed to affect only the incubation period (Appendix II.5.11).

7. The split of infectivity between the blood components is taken as 24% in red cells, 22% in buffy coat, 54% in plasma, based on the low dose experiment of Brown et al 1998 (Appendix II.3.6). An alternative approach giving the lowest infectivity in plasma would be based on the white cell content, giving a split of 13% in red cells, 87% in buffy coat, 0.1% in plasma. Another alternative, giving the highest infectivity in red cells, would be based on the spiking experiment of Brown et al, giving a split of 68% in red cells, 22% in buffy coat, 10% in plasma.

8. The split of infectivity between the plasma fractions is 12.4% Cryoprecipitate, 7.1% Fractions I & III, 0.3% Fraction II, 2.4% Fraction IV and 0.7% Fraction V, based on a combination of Brown's low dose experiments in 1998 and 1999. An alternative approach giving the lowest infectivity in plasma fractions would be based on the spiking experiment alone, giving a split of 0.7% in cryoprecipitate, 0.8% in Fraction I, II and III, 0.006% for Fraction IV and 0.0004% in Fraction V. Another alternative, giving the highest infectivity in plasma fractions, would be based on the low dose experiment alone excluding lost infectivity (this assumes no infectivity in the

cryosupernatant) giving a split of 54% in cryoprecipitate, 30.5% in Fraction I & III, 1.5% Fraction II, 10% Fraction IV and 3% in Fraction V.

9. Calculating infectivity in plasma derivatives was considered using one of three possible approaches identified in this report. Assuming that the infectivity in the plasma derivatives is proportional to their protein content was not considered scientifically sound by the expert committees consulted. A different method is used based on clearance factors (Appendix II.4.3.1). A worst case scenario is also assessed. One alternative is to use different approaches for different scenarios.

10. 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. This study assumes that the cumulative effect of repeated doses over a one year period will be additive, but ignores doses received after the first year.

11. 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).