



vCJD INFECTION RISKS OF BONE PRODUCTS FOR REVISIONARY HIP REPLACEMENT

Issue

1. The National Blood Service (NBS) together with the Department of Health's Economics and Operational Research (EOR) division have produced a draft risk assessment to examine the risk of transmission of vCJD via implantation of bone.

Background

2. This risk assessment follows on from previous work by EOR on the risks of transmitting vCJD via donated blood, hospital surgery and dentistry, all of which have been endorsed by SEAC. It also results from a continuing programme of collaboration with NBS, in which EOR provide analysis of issues around the safety and supply of blood and tissues.
3. The main use of bone is in revision hip procedures (where an artificial hip is replaced after having worn out or become loose). Bone is sourced from either single femoral heads (from living patients undergoing primary hip replacement) or from cadaveric donors. Bone products may be sourced from the NBS or other bone banks. Alternatively bone in the form of individual femoral heads may be taken and pooled in theatre at the time of operation.
4. The risk assessment compares the risks associated with different bone products i.e. processed or unprocessed, pooled or unpooled, under different scenarios of vCJD infectivity.
5. There are major uncertainties as to whether a donor incubating vCJD would carry infectivity in bone tissue, marrow or blood. The draft risk assessment has been carried out on the precautionary assumption that 100% of the infectivity is present in blood and bone marrow.

6. Processing of bone removes a large proportion of the blood and marrow thus reducing this possible source of infectivity (Lomas *et al* 2000). However the processes most effective in removing blood and marrow require pooling of several donations if living donations are used (though not for cadaveric donations, where larger quantities can be obtained per donor).

List of accompanying material

- **Annex 1** An NBS introduction to the EOR Bone risk assessment paper July 2003.
- **Annex 2** vCJD infection risks of bone products for revisionary hip replacement.
- **Annex 3** Paper by Lomas *et al* on processing of whole femoral head allografts.
- **Annex 4** Update on mouse infectivity studies from the IAH neuropathogenesis unit.

Advice sought from the committee

7. Does the committee agree with the scenarios used regarding the possible distribution and levels of infectivity present in blood, bone marrow and bone?
8. Are the calculations and conclusions presented consistent, and compatible with current scientific knowledge?
9. Does the committee have any specific views on:
 - the potential infectivity of bone marrow relative to that of blood?
 - the possibility of significant infectivity appearing in bone?
 - possible effects of gamma-irradiation in reducing infectivity?
10. In the published tests of processed bone, are the markers used to determine the effect of processing adequate to assess loss of potential vCJD infectivity?
11. Is the committee aware of any published or prepublication data that may affect the outcome of this risk assessment?



NBS TISSUE SERVICES

An NBS Introduction to the EOR Bone Risk Assessment Paper July 2003

INTRODUCTION

Tissue banking has grown within the National Blood Service (NBS) since the early 90's, utilising the donor selection, donation testing and quality system expertise already established for blood. The growth has resulted from both the development of tissue banking services by individual blood centres in response to local clinical demand and the decision by a number of well established banks to become part of the NBS. Tissue Banking in Scotland is confined to the SNBTS, which also provides a multi-tissue bank service.

NBS Tissue Services is now the largest multi-tissue banking organisation in the UK. However it is not a monopoly supplier and there are a small number of other cadaveric tissue banks and a larger number of surgical donation programmes run from within hospitals (latest figures collated for the BATB (British Association of Tissue Banks) indicate over 3000 femoral heads (FH) collected independently). NBS is a significant leader in the development of national and international standards, policies and regulation in the field. The policies and procedures used in non-NBS banks are not described here.

DONATION PROGRAMMES

NBS Tissue Services runs two major donation programmes, run by a team of about 20 highly trained senior nurses.

- **Surgical bone donation**

Femoral heads are removed during primary hip replacement and banked for future use by other patients. This programme requires close co-operation with over 70 collaborating hospitals. Around 4 - 5,000 donations are collected by the NBS each year.

- **Cadaveric tissue donation**

Bone, tendons, skin and heart valves are retrieved from donors after death (see later section for clinical uses). NBS tissue retrieval teams go to the mortuary to carry out the retrieval

TISSUE PROCESSING AND CLINICAL USE

A proportion of femoral heads is issued for use without processing, as long as the results of bacteriology testing are negative. The remaining surgical bone donations, and all cadaveric bone donations, are processed and/or sterilised before issue. Processing involves washing and shaping or grinding followed by either freeze-drying or deep freezing, with exposure in the final packaging to either ethylene oxide or gamma irradiation. Processing of femoral heads involves the pooling of 17 femoral heads together. Pooling of cadaveric bone donations is not undertaken because there is sufficient bone in a single cadaveric bone donation for it to be feasible to process from one donor at a time. Surgeons using individual femoral heads pool bone in theatre at the time of operation. Theatre pooling techniques vary between individual centre preferences and may or may not include a washing step.

The great majority of bone is used during joint revision surgery. The development of impaction grafting techniques has caused significant growth in the clinical demand for unprocessed femoral heads, which are morcellised by the surgical team in theatre, and also for processed ground bone produced in the Tissue Services facilities (Figure 2).

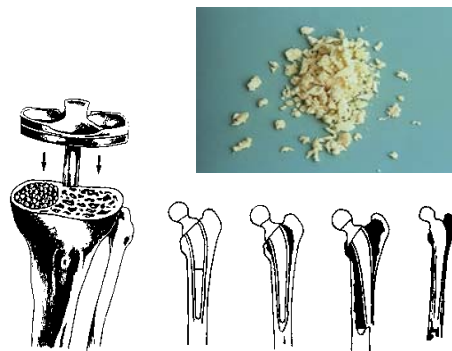


Figure 2: Bone impaction grafting in revision joint surgery

BONE PROCESSED PER ANNUM BY TISSUE SERVICES

Bone donations are processed in the following proportions:

- 1500 unprocessed surgical FH which surgeons process in theatre.
- 800 irradiated but otherwise unprocessed surgical FH which surgeons process in theatres.
- 1000 surgical FH are processed in pools.
- 200 cadaveric bone donations processed to produce 1500 surgical FH equivalents.

**vCJD INFECTION RISKS OF BONE PRODUCTS FOR
REVISIONARY HIP REPLACEMENT**

**Economics and Operational Research (EOR4) Division
Department of Health**

Version 1.0: 25th July 2003

1. Background

- 1.1 This note sets out an assessment of the relative vCJD infection risks of the various forms of bone supplied by NBS and SNBTS for revisionary hip replacement grafts (by far the most common use of donated bone). We have included additional analysis contributed by colleagues at SNBTS regarding batch dedication and product volumes.
- 1.2 The analysis examines the following products supplied by NBS and/or SNBTS.
 - 1. Unprocessed Femoral heads from living donors
 - 2. Single, Washed and Centrifuged Femoral heads from living donors
 - 3. Morcellised Freeze dried, gamma irradiated bone pooled from 17 living donors
 - 4. Morcellised Freeze dried, gamma irradiated bone taken from 1 cadaveric donor
 - 5. Morcellised Frozen, gamma irradiated bone pooled from 17 living donors
 - 6. Morcellised Frozen, gamma irradiated bone taken from 1 cadaveric donor
- 1.3 The morcellised frozen and freeze-dried bone from both the cadaveric and living donors (products 3 to 6 above) are produced in two pack sizes, as shown in Table 1 below. The freeze-dried products are approximately half the weight and volume of the frozen products as a consequence of the freeze-drying process. However the original volume of both products is the same, and the amount of residual marrow in each product is assumed to be the same.

Table 1 – Product information provided by NBS (per pack/unit)

Product	volume (cc)	weight (g)	marrow (ml)	units used
Femoral heads - unprocessed		80	15 to 20	2 or 3
- washed/ centrifuged			#	2 or 3
Frozen processed bone –	70	32	#	2
17 Femoral heads or 1 Cadaveric	35	16	#	4
Freeze-dried processed bone –	35	13	#	2
17 Femoral heads or 1 Cadaveric	15	5.5	#	4

These figures are estimated later in the paper

- 1.4 NBS have available estimates of the number of procedures carried out using each type of product, the average age of the patients and their post-operative mortality rate. In this context, it should be noted that while the patients were generally elderly they are selected as being fit before they are submitted for this type of operation. If infected with vCJD then, such patients might well live long enough to develop symptoms of the disease. There are also a small number of patients under 20 years (<0.1%) who undergo this procedure for Juvenile Rheumatoid arthritis (Still's disease).

2. *Product infectivity and infection risks per unit used*

Baseline assumptions

- 2.1 The calculations given here are illustrative and are based on a number of assumptions. The most important of these is that bone itself does not carry vCJD infectivity¹, so that any infection risk would be caused by marrow or blood. NBS data show that an unprocessed femoral head may contain a mixture of marrow and blood amounting to 15-20ml, and we take the higher figure for illustration. We also suppose that some residue of marrow/blood may be left despite processing. For the morcellised frozen and freeze-dried products, NBS information is that no residue is detectable, and that this would imply removal of at least 99% of the amount originally present in an unprocessed head. SNBTS is currently developing the washed/centrifuged product, and estimate that this process should be capable of removing 98% of the marrow/blood originally present. These figures are used here for illustration, though subject to sensitivity analysis.
- 2.2 We have assumed 2ID_{50s} to be the level of infectivity at which the infection of a recipient is considered to be certain. Below this dose, we use the linear dose-response model to calculate the chance of infection [Chance of infection = ½ * dose received, in ID_{50s}]. This follows previous work on vCJD infection risks for blood and blood products carried out both by EOR and risk consultants DNV. The simple linear model has previously been endorsed by SEAC as a sufficiently good working assumption unless or until any contrary experimental evidence emerges.
- 2.3 We considered the possibility that the potential infectivity of marrow was proportional to its cellular content and therefore higher than that of blood. This is a suggestion on which further expert comment would be welcome. However comments received from Prof James Ironside² [CJD Surveillance Unit,

¹ The most recent (2003) WHO Guidance on TSEs lists bone as having “no detected infectivity”, though the only tests noted are of BSE in cattle.

² On bone marrow, Prof Ironside commented: ‘... there is very little data on this subject. I do not think that it is necessarily logical to argue that if blood is infectious, then bone marrow may be more infectious in proportion to its cellular content. The cells of the bone marrow may not be able to support location of abnormal PrP, which appears to be confined to follicular dendritic cells in ‘organised’ lymphoid tissues. Admittedly, since scrapie infectivity has been transmitted by transfusion of buffy coat, there are implications that the cellular fraction of blood may be

Edinburgh University] cast doubt on this argument. We have therefore started with a scenario in which its potential infectivity is the same as that of blood, this in turn being as suggested in the most recent study commissioned by Department of Health from DNV. This gives a baseline estimate of 2ID₅₀/ml for the blood/marrow mix within a femoral head. However much higher and lower figures are also considered below, reflecting the current scientific uncertainty on this point.

Infection risks per unit

2.4 In considering risks to the recipient population, we take single femoral heads and the larger packets of the two processed products (70cc frozen or 35cc freeze-dried) to be essentially equivalent “units”, with the total number of units of all types used being constant. The key consideration is then the *risk per unit used*, against a given prevalence of infective donors. The prevalence of vCJD is assumed to be the same for living or cadaveric donors.³ It is also assumed to be small – e.g. not more than 1 in 100 donors being infective – meaning that the chance of any individual receiving bone from *more than one* infective donor will be vanishingly small. (For higher prevalences, the model would slightly overstate the number of new infections caused, particularly by pooled products.) However no specific assumption is made as to how high or low the prevalence of vCJD might be – the aim being to clarify the relative risks associated with each product.

2.5 Table 2 considers infection risks per unit used. Each Femoral Head is assumed to contain 20 ml of marrow/blood initially, with an infectivity of 2 ID₅₀ / ml. The unit infectivity of the freeze-dried products is equivalent to their corresponding frozen products, so both are classified together as ‘processed’.

Table 2 – Probability of infection per unit of bone used

PRODUCT	Dose per infected unit (ID₅₀)	Probability of dose being present	Chance of Infection per unit used
Unprocessed FH	40	1p	1p
Centrifuged FH – 98% removal	0.8	1p	0.4p
Processed - 17 FH 99% removal	0.033	17p	0.28p
Processed - 1 cadaver 99% removal	0.033	1p	0.28p

infectious, but the data for this in humans with variant CJD is lacking so far. I therefore think that it would be prudent to be cautious [and to]... assume a range of possibilities’.

³ The comparative youth of cadaveric donors might make some difference here. Both living and cadaveric donors have about a 30% higher than average chance of previous transfusion. If this increases the chance of having been infected, the prevalence of the disease might also be higher than in the general population. But this would affect both sets of donors (roughly) equally, and would not affect the relative risks of the different bone products.

IN STRICTEST CONFIDENCE

2.6 Calculations are set out in more detail in Box 1 below. In each case, the chance of infection is governed by:

- The dose present in a unit *if* it contained bone from an infected donor – with any dose of $2ID_{50}$ or above assumed to cause certain infection, so that further increases have no effect on infection risks.
- The probability of the unit containing bone from such a donor. For unpooled products, this will simply be the prevalence of infective donors (say p). For pooled products, it will be p *(number of donors in the pool).

Box 1: Basis of calculations

(a) Unprocessed Femoral Heads

Each infected head would contain a dose of 40 ID₅₀ (more than sufficient to infect for certain), this occurring with probability **p**. So chance of infection = 1 * **p**

(b) Washed / Centrifuged Heads

Following removal of 98% of blood / marrow, an infected head would contain a residual dose of 0.8 ID₅₀, entailing a 0.4 risk of infection. This would again occur with probability **p**. So chance of infection = 0.4 **p**

(c) Pooling from 17 living donors

Suppose each pool of 17 is used to make 12 units of processed bone. If one donation is infected, it will contain 40 ID₅₀ before processing. Assuming 99% is removed and the residue split equally between the 12 units, each will contain a dose of (40/12 * 1/100) ID₅₀.

The chance of any 1 of the 17 heads being infected is 17 **p**.

So the chance of infection per unit used = $\frac{1}{2} * 40/12 * 1/100 * 17 \mathbf{p} = 0.28 \mathbf{p}$

(d) Pool from single cadaveric donor

On average, the bone obtained from each cadaveric donor is approximately 2/3 the mass of that in a pool from 17 living donors. (This is reflected in the fact that 8 units are obtained, as compared with 12.) We assume that the percentage of marrow/ blood is similar to that in femoral heads from living donors, and that the processing has the same effect as regards the residue left. So if the donation is infective, it would initially contain (40 * 2/3 * 17) ID₅₀.

If processing removes 99% of this, each of the 8 units obtained would carry a dose of (40 * 2/3 * 17 * 1/100 * 1/8) ID₅₀.

There is a probability **p** of the donation being infected

So the chance of infection per unit used = $\frac{1}{2} * 40 * \frac{2}{3} * 17 * \frac{1}{100} * \frac{1}{8} \mathbf{p} = 0.28 \mathbf{p}$.

Note:

The above calculations assume that the loss of material implied in the 17 – 12 conversion of heads to packets implies no loss of infectivity: this may be overly-pessimistic. Similarly for the loss of material during processing of cadaveric donations. A more detailed examination of the processing methods might allow for more precise estimates, but may be of limited practical value given gross uncertainties around potential infectivity of the materials.

3. *Alternative Scenarios for Infectivity*

3.1 We have stressed the uncertainties attaching to the potential infectivity of blood / marrow. Infectivity in human blood has not been conclusively demonstrated while (on the other hand) that of marrow might be significantly higher. So we now explore the effects of lowering or raising the assumed infectivity of the marrow / blood mix. Results are as shown in Table 3, with the shaded row representing the original baseline scenario.

Table 3 : Chance of infection per unit of bone used, for different levels of blood/marrow infectivity

Infectivity (ID ₅₀)		CHANCE OF INFECTION PER UNIT USED			
Per ml marrow	Per femoral head	Unprocessed	Centrifuged (98% removal)	Processed (99% removal)	
				17 living	1 cadaver
0.01	0.2	0.1p	0.002p	0.0014p	0.0014p
0.1	2	p	0.02p	0.014p	0.014p
1	20	p	0.2p	0.14p	0.14p
2	40	p	0.4p	0.28p	0.28p
5	100	p	p	0.71p	0.71p
10	200	p	p	1.42p *	p
100	2000	p	p	14.2p *	p
≥ 120		p	p	17p *	p

(* indicates risk would be reduced by batch dedication – see below)

3.2 Some general points are illustrated by the table. For *lower* levels of infectivity:

- The risks associated with all products reduce proportionately, *except* for unprocessed femoral heads.
- For unprocessed heads, the unit dose falls below 2 ID₅₀ (reducing the infection risk) only once the infectivity of marrow / blood is below 0.1 ID₅₀ per ml.
- Consequently, the differential between unprocessed heads and all other products is greatest for lower-infectivity scenarios.

3.3 For *higher* levels of infectivity:

- Risks from unprocessed heads are already at their theoretical maximum in the baseline scenario (certain infection if the head is infected), so cannot increase further.
- Centrifuging ceases to reduce infection risks once the residual dose reaches 2 ID₅₀: with 98% removal, this occurs at a marrow/blood infectivity of 5 ID₅₀ per ml.

- Risks from the pooled products increase to a theoretical maximum of $17 p$ (i.e. $p * \text{number of donors in pool}$) per unit used. This occurs when the infectivity in each unit reaches $2 ID_{50}$, requiring an infectivity level of $120 ID_{50}$ per ml of blood / marrow.
- Consequently, the disadvantages of pooling are seen in these high-infectivity scenarios, eventually being sufficient to overcome the benefit of processing.

4. *Further Comments*

Pooling of donations

- 4.1 The effect of pooling depends on the level of infectivity. If this is low enough for the doses received never to exceed $2 ID_{50}$, pooling is in principle irrelevant to the expected number of infections for a given donor prevalence. *Without pooling*, any infective donation will go to only one recipient. *With pooling*, several (in this example, 17) recipients would be exposed, but each would receive a smaller dose. But with a linear dose-response model, these effects cancel out. Within the population of recipients, pooling will affect the distribution of risks, but not the eventual number of infections to be expected.
- 4.2 If infectivity is so high that even after processing, the dose from one infected donation in a pool would exceed $2ID_{50}$, the risk of infection is governed by the number of donors in the pool. This is demonstrated in the last row of Table 3, in which the pooled product would carry 17 times the per-unit risk of any unpooled alternative. However it should be stressed that processing may in fact remove more than 99% of blood / marrow: the 1% residue is intended as an upper limit. If the residue were less, this effect of pooling would only occur at still-higher levels of initial infectivity.

Batch dedication

- 4.3 Provided doses received remain below $2 ID_{50}$, batch dedication (ensuring that contributions from the same donors go to the same recipients) again affects only the spread of the risk, not the expected number of infections. For example, if all units were given in pairs from the same donor rather than from separate individuals, half as many individuals would be exposed to twice the risk of vCJD infection.
- 4.4 In most scenarios, infection risks per procedure would remain in proportion to the number of units used - e.g. using two would units double the risk to the individual patient - with or without batch dedication. However in those high-infectivity cells marked * in Table 3, the dose received from 2 infected units would exceed $2 ID_{50}$, and batch dedication of units will limit the maximum possible number of infections to $17 p$ *per procedure* (rather than per unit).

Caveats

- 4.5 This analysis is based on a number of assumptions on topics where information is lacking. The most significant is that vCJD infectivity would be confined to bone / marrow. If significant levels were to be carried in the bone itself, then processing of the product would become irrelevant and the most important consideration in reducing risk would be the avoidance of pooling. (In this respect, results would resemble those at the bottom of Table 3.)
- 4.6 Aside from the uncertainties around the infectivity of bone / marrow / blood, this analysis is based on a simple “piecewise linear” dose-response model, in which infection is regarded as certain for any dose at or over 2 ID₅₀. From analogy with other disease models, it appears more plausible that certainty would be approached gradually. (In other words, with effective certainty only reached at higher doses).
- 4.7 Also, no account has been taken of the possible effect of higher doses in shortening the incubation period of the disease once infection has taken place, making those infected with higher doses more likely to suffer vCJD symptoms rather than dying of other causes first.
- 4.8 Both these last two points provide further arguments for avoiding products that may carry high individual doses of infectivity – primarily unprocessed femoral heads.

5. Conclusions

- 5.1 Though significant uncertainties remain, this paper has compared the risks of the various bone products across a wide range of scenarios. Given that pooling of products is never advantageous, a point of particular interest is the balance between its disadvantages and the advantages of processing in removing the material most likely to carry infectivity. As we have seen, this balance depends on the presumed infectivity initially present. However in most of the scenarios considered here, the per-unit vCJD risks from the pooled, processed product are substantially lower than from unprocessed femoral heads.
- 5.2 From the point of view of vCJD risks, use of unprocessed femoral heads is the least preferable option in many scenarios. Their continued use might however be justifiable on other grounds – e.g. superior mechanical properties – lying beyond the scope of this analysis. This would require further discussion.
- 5.3 The most robust options for minimising vCJD risks are those that involve removal of blood / marrow *without* pooling of donations. Throughout, no other product is less risky than that processed from a single cadaveric donor. (A further potential advantage is that it may become feasible to screen cadaveric donors for vCJD using tests that would be impracticable for living donors.) Washing and centrifuging of individual femoral heads also represents a robust option that may meet the preferences of clinicians, though the removal of blood / marrow appears likely to remain less complete than with the morcellised processed products.

Lomas R, Drummond O, Kearney JN. Processing of whole femoral head allografts: a method for improving clinical efficacy and safety. Cell Tissue Bank. 2000;1(3):193-200.

http://www.ncbi.nlm.nih.gov/pubmed/15256945?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum



UPDATE ON MOUSE INFECTIVITY STUDIES FROM THE IAH NEUROPATHOGENESIS UNIT

Issue

1. Preliminary data on the experimental studies investigating the infectivity of bone marrow derived from vCJD patients has been provided by Professor Moira Bruce (IAH). The data has been provided to assist the Committee in considering the EOR risk assessment. The data are unpublished and is produced in confidence to the Committee.

Background

2. A series of experiments is in progress examining the infectivity of vCJD tissues, including; spinal cord, CSF, appendix, lymph node, peripheral nerve, dorsal root ganglia, trigeminal ganglion, and bone marrow. Bone marrow samples from three vCJD patients and one non-TSE control have been injected into groups of mice.
3. Mice (RIII n=24) were intracerebrally inoculated with 20 μ l 10% (physiological saline) vCJD bone marrow homogenate. The development of neuropathologically confirmed clinical TSE disease or the presence of TSE neuropathology in mice culled with inter-current disease have been used as indicators of transmission.
4. Only one of the vCJD bone marrow bioassays is far enough advanced to give meaningful results. Mice in this experiment have been negative up to approximately 760 days post inoculation (dpi). The analysis of this experiment is not yet complete, as some mice are still alive, but previous experience indicates that it is extremely unlikely that mice surviving this long after vCJD challenge will show any signs of being infected. The other two vCJD bone marrow bioassays are currently negative at 335 and 336 dpi; only high infectivity tissues such as brain would be expected to produce disease in mice within this timescale. After approximately 780 days bone marrow from the control patient is negative for infectivity.
5. The single result using bone marrow inoculum shows that this tissue has a lower level of infectivity than the peripheral nervous ganglia, spinal cord, lymph node, spleen and tonsil.

6. The limit of detection of the mouse assay should be considered when interpreting these preliminary results. A negative result does not indicate an absence of infectivity, only that the infectivity level is below the threshold of detection by the relatively inefficient mouse bioassay.
7. SEAC will be updated on the results of these vCJD mouse infectivity studies once the remaining groups have been examined.