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REPORT

Evaluation of the risk of transmission of Creutzfeldt-Jakob agent by blood and its constituents

Experts' group meeting of 16 November 2004

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I. INTRODUCTION

Analysis of the risk of transmission of vCJD agent by products derived from human bodies and in particular blood and its constituents, has been annually updated since the initial report of December 2000. The latest update, dated February 2004, was motivated by publication of the first case of probable transmission of vCJD by transfusion, reported in England in December 2003.
There have been other events since February 2004, justifying review of evaluation of vCJD risk in the light of these new findings. The following are worthy of note:

- publication of a second probable case of transmission of vCJD agent by transfusion in a British patient (case published in July 2004),
- decision of the British health care authorities, in order to decrease the risk of "secondary transmission" (inter-human transmission) of vCJD, to establish exclusion measures for certain patients receiving blood products (labile blood products (LBP) and, under certain circumstances, blood-derived medicines (BDM)) obtained from donors having developed vCJD after a donation, classifying them as at-risk individuals regarding blood, organ or tissue donation, as well as certain surgical procedures. Establishment of these precautionary measures and exclusion around these at-risk individuals led the British health care authorities to inform patients having been treated with these products,
- notification of the eighth and ninth French cases of vCJD, each of these patients having been a blood donor on several occasions, in the periods 1993-2003 and 1984-2002 respectively. [NB.: it should be noted that information on the ninth case was sent to the experts during the meeting, the case having been confirmed the day before the meeting by the CJD monitoring system in France.]

The latest update of the report (February 2004) stated that "... *the risk of transmission* [by blood] *cannot be ruled out, and in a conservative approach, must be considered no longer as a theoretical but rather a possible risk*". Concerning different types of blood products, the report states that: "... *on the risk scale the respective positioning of LBP* [labile blood products used in transfusion] *and BDM* [blood-derived medicines, obtained by fractionation of plasma] *remain unchanged. LBP appeared to be more at risk, preparation procedures not being sufficient to ensure the safety of such products, if an initial donation proved to be contaminant ... BDP prepared from plasma undergo, during fractionation, a number of stages which increase their level of safety accordingly*".
However, the fact of access to information according to which a donation obtained from a donor subsequently developing vCJD has been used in transfusion or included in fractionation, requires once again opening up the discussion on the question of risk of secondary transmission by transfused patients and by patients treated with BDM, as well as coping with this risk, notably in terms of information for prescribers and patients having received various blood derivatives obtained from donations now identified as being at risk.
The British authorities finally adopted, with the objective of reducing the risk of secondary transmission from individuals exposed to blood products, a strategy for the routine communication of information to the transfused individuals. They also decided to inform retrospectively patients treated long-term with BDM prepared from plasma collected in the United Kingdom between 1980 and 1997 (date at which fractionation of BDM was done only using plasma collected in the USA).

In this context, a group of multidisciplinary and independent experts (*Annick Alpérovitch, Elisabeth Bouvet, Jacques-Christian Darbord, Jean-Philippe Deslys, Marc Eloit (Chair), Claude Guérois, Jenny Goudemand, Joseph Hajjar, Norbert Ifrah, Corinne Lasmézas, André Lienhart, Claude Négrier, Yvette Sultan)* met 16 November 2004 and once again was questioned on the evaluation of the risk of transmission of vCJD by products obtained from a human body, and

notably blood products, in order to propose if necessary any new measures deemed useful to decrease the risk of secondary transmission of this agent responsible for transmissible subacute spongiform encephalopathy (TSSE).
This report was prepared by the Afssaps (French Agency for the Safety of Health Products) and validated by the experts following the meeting.

II. NEW EVENTS

II.1 Risk of transmission by transfusion: two "transfusion" cases reported in the United Kingdom

The two British "transfusion" cases are the essential event needing to be taken into account when reevaluating the risk of transmission of the pathological protein (PrPres or prion[1]).
The first case has already been discussed in the February 2004 report. It was interpreted by the British as being very probably of transfusion rather than dietary origin. There was the concomitant presence of two events sufficiently rare for probability of dietary origin to being very slight: both the donor and the recipient developed vCJD. In addition, the relatively unusual age (recipient aged over 60, while the mean age of onset of vCJD is 28) would be suggestive of a transfusion origin. The latest update of the report, in February 2004, was motivated by this case. While in the February 2000 report, the risk of transmission had been described as being theoretical, on the basis of this first case, the February 2004 report re-defined risk as "possible".
The second "transfusion" case was reported in the United Kingdom during July 2004. This case presented differently from the first, in that death was not attributable to vCJD, and there were no clinical signs of the disease and hence infectivity. It was only the presence of PrPres in anatomical specimens of peripheral lymphoid tissues (no prion in central nervous system) which enabled confirmation that the subject was a carrier of the agent and clinically asymptomatic. For the first time in the cohort of subjects carrying the pathological protein, the subject was codon 129 heterozygous. The experts considered that this case, beyond questions which it raises as actual imputability of transfusion, does not enhance the demonstration of transmission by transfusion and does not offer any new information in this problematic area in which the only event of importance is the fact that patients transfused with the blood of donors who have developed post-donation vCJD develop the disease or are positive for PrPres in their lymphoid tissue. In contrast, this probable case of transmission of the agent by transfusion in a heterozygous individual could confirm that the intravenous route is effective in transmission of the agent, thereby supporting the working hypothesis of February 2004 which considered that the intravenous route was just as effective as the intracerebral route.

Onset of these two transfusion cases which must, in a conservative approach and despite the various reservations expressed, be considered to be proven, leads the experts to define more explicitly the risk of transmission by blood products considering it to be probable and no longer possible.
However two specific points must be made:

- These British cases concern the transfusion of non-de-leukocyted LBP. However in view of what is now described as to the moderate efficacy of leukoreduction (see III.1) in decreasing infectious load which seems to be distributed not only in white cells (buffy-coat) but also in plasma, it must be considered that the risk (of the presence of the infectious agent in blood, and hence of transmission) applies to LBP in general, whether de-leukocyted or not.

[1] - This report will use all of the abbreviations and pathophysiological data concerning the agent without redefining them. These abbreviations and data were established in the December 2000 report.

- However these cases do not enable accurate estimation of the risk of transmission of vCJD by LBP. Up till now, two probable cases of transmission have been diagnosed (including only one which developed the disease) in the cohort of 48 English recipients of LBP obtained from vCJD donors. More accurate quantification of the risk of transmission of vCJD by LBP will requires a longer observation period and taking into account the bias related to the rapid death of transfused patients (in France, about half the patients died within the year following a transfusion). In France, no case of transmission has been reported in the cohort of 26 patients transfused with labile blood products derived from donations of the eighth and ninth cases of vCJD in France (some transfusions were given more than 10 years before). It may also be pointed out that in animal models in which transfusion transmission has been sought (notably the work of Houston et al.), the transmission rate varies from 0 to 40%.

Regarding LBP, identification of the risk of transmission as "probable" must be understood as indicating that there are transfusion cases considered to be "proven", without it being possible to make pronouncement as to the frequency of such transmission, nor risk factors, notably the date of donation in relation to the date of onset of symptoms in the donor (see III.5.2).

Regarding BDM, no proven case of transmission has been reported either in the United Kingdom, France or any other country, while several hundred batches of BDM and millions of units have been administered. This maintains the hierarchy established in the 2000 report between LBP and BDM, the latter having a lower level of risk.

II.2 Other scientific data

Overall, scientifically speaking, there are no new experimental nor epidemiological data which, since February 2004, would considerably modify knowledge on the agent, its pathophysiology or mode of transmission.
Data on which evaluation of the risk of transmission by products derived from the human body is based, published in February 2004, remain valid (even though hypotheses expressed were deliberately pessimistic and still remain pessimistic despite progress in epidemiological data (see II.3)).
Appendix 1 cites the main publications between February and November 2004.

II.3 Epidemiological data

II.3.1 Variations in epidemic curves of vCJD

The annual incidence of vCJD in the United Kingdom has now tended to decrease for three consecutive years, after a peak which seems to have been reached in 2000. At present, all cases are codon 129 Met/Met homozygotes. In France, because of the small number of cases, it is not possible to identify any tendency in the curve of incidence nor detect a peak (nine cumulative cases in France as against 151 in the United Kingdom, as of 16 November 2004). Data concerning exposure to the BSE agent suggests that the "peak" could be later in France and it will probably be more difficult to assess in view of the very small number of cases.
The fact that three cases of vCJD had been notified in France in the past 11 months up to November 2004, does not indicate that the epidemiological situation compared between France and the United Kingdom has changed, the ratio of 1 to 20 between France and the United Kingdom is probably the result of difference in dietary exposure and overall remains the same. This report must be estimated on the total number of cases reported in the two countries during the past 9 years, and not on cases notified this year. The very small numbers notified in France

naturally are a source of fluctuations which must not be interpreted erroneously as a major modification of the tendency in France.
Very recently, using estimations of distributions and values of parameters established for the British population, Chadeau estimated the expected number of cases of vCJD in the French population by age cohorts (Int J Epidemiol, in press). The model predicts several tens of cases (mean 33, upper limit of 95% CI: 98) including 2/3 in the population born after 1969 and 1/3 in those born between 1940 and 1969. These new estimations are less pessimistic, despite the estimation of the December 2000 report which envisaged about 300 cases in the next 60 years.

II.3.2 Asymptomatic carriers

The second British case, reported in July 2004, has two special features requiring discussion here.

i) Contamination of the recipient was not identified by the development of the disease, but rather by the demonstration of PrPres in an autopsy specimen, this autopsy having been done since the patient was included in the closely-monitored cohort of 48 recipients of LBP obtained from donors with vCJD,
ii) in addition, this subject was codon 129 heterozygous and there was nothing to indicate that he would have finally developed the disease nor after what latency of incubation.

This case raises the question of the possible existence of "silent carriers" and in particular heterozygous individuals. These carriers might constitute an unknown reservoir to the disease.
In view of the relative effectiveness of the transfusion route, an unknown reservoir among donors (heterozygous or not) in process of incubation would already have led to a larger number of cases of transmission in the group of transfused individuals than these two solitary cases emerging from the English cohort of 48 recipients of LBP obtained from vCJD donors.
The size of this population of infected asymptomatic subjects is not known. The following factors could help in creating some hypotheses on its order of grandeur:

1. Regarding the codon 129 Met/Met population, several studies (Huillard d'Aignaux and Cooper in the United Kingdom, Chadeau in France) have estimated by modelling not only the number of cases of vCJD but also the number of people infected. According to Cooper and Chadeau, using a distribution of the length of incubation in Met/Met individuals similar to that suggested by Valleron, the number of persons infected (including future cases of vCJD) is greater than the expected number of clinical cases, but is of the same order of grandeur, i.e. a few hundreds in the United Kingdom and a few tens in France. Because of the distribution of the duration of incubation of the disease and age-related susceptibility, bias due to death by another cause is low. According to Huillard d'Aignaux, the upper limit of the 95% CI of the number of infections in the British population varies according to the model and the duration of incubation of vCJD between 1,000 (median incubation: 11.7 years) and 25,000 (median incubation: 17-20 years).
2. There is no argument for considering that the risk of infection in Val/Val and Met/Val individuals might be greater than that of Met/Met. If the risk of infection is independent of genotype, the estimation summarized in point 1 can be broadly extrapolated to other genotypes subject to the condition of the distribution of genotypes in the population (40% MM, 60% other genotypes). The recent work of Valleron (oral presentation at the GIS meeting "Prion infections", INST, Saclay, France, November 2004), predicting using the most pessimistic

hypothesis of a few hundred non-Met/Met clinical cases in the United Kingdom are consistent with this analysis.

3. Study of the prevalence of accumulation of PrPres in lymphoid tissues (notably publications of Hilton et al., 2004), leads to estimations compatible with the above. Taking all genotypes together, the estimated number of individuals in the process of incubation in the susceptible population (between 10 and 30 years of age at the time of the surgical procedure enabling the collection of tonsil or appendix biopsies) is 3,808 (95% CI: 785-11,128). [NB.: An individual with PrPres in a lymphoid organ is considered to be in the process of incubation but may never develop the disease.] Regarding the French population, and with the hypothesis of less dietary exposure to BSE risk, these estimations must be divided by 10 or 20.

Hence, estimations of the size of the infected population (and hence incubation of vCJD) lack precision. Despite this lack of precision, values obtained by different approaches are fairly consistent. Overall, results suggest that the infected (by dietary exposure) asymptomatic population is not very large (a few hundred cases in France). These estimations confirm that the hypotheses adopted in 2000 were reasonable and do not require revision today, although they deliberately and for conservative reasons, remain pessimistic.

The population of transfused patients who might have been exposed by transfusion to the infectious agent and could more surely be receptive to a secondary transmission in view of the effectiveness of the IV route, also needs to be considered.

This population of individuals no longer poses any problem for blood donation from which they are excluded, though the question arises of the risk of secondary transmission from organ and/or tissue donations. The marked "censure" affecting this population explains difficulties in assessing the risk of transmission by transfusion, and starting from that the degree of risk of secondary transmission.

III. RE-ANALYSIS OF THE RISK OF TRANSMISSION OF vCJD BY BLOOD AND ITS CONSTITUENTS, IN FRANCE

It was stated in the February 2004 report that the first English transfusion case did not modify the level of risk of exposure to the infectious agent by blood products, as considered and estimated in the December 2000 report. The December 2000 report accepted as primary hypothesis that blood was infectious and that the infectious agent could hence enter the transfusion chain and/or initial plasma used for the fractionation of BDM.

The level of risk for finished products (LBP or BDM) suggested as early as December 2000, did take into account the use of contaminated donations. Onset of these two English transfusion cases implies that the level of risk, which had been estimated taking this hypothesis into consideration, now applies to a real and no longer hypothetical situation.

The fact that the two cases of vCJD recently notified in France (8th and 9th cases) were blood donors is not an unexpected event. In view of the proportion of blood donors, whether regular or not, in the population as a whole, it is only to be expected on the basis of a certain number of cases of vCJD in France that blood donors will be found among new cases notified.

The principle used for calculation and initial hypotheses for estimation of the degree of risk are hence unaffected, the same applying consequently to the levels of risk proposed for the different products.

III.1 Transfusion products

Regarding transfusion products, it is estimated that regardless of the LBP considered and the fact that procedures leading to the final product transfused to the patient do not have sufficient ability

to eliminate the infectious agent, the risk of transmission by one of these products is similar to the risk of having, within the donor population, a donor incubating vCJD at the time of donation. On the basis of estimations of the number of cases expected in France in the coming years (300 cases in the next 60 years - see December 2000 report), the risk is estimated at 1/120,000 donations. Chadeau's model, together with all recent models of the British epidemic, would lead to downward revision of this risk (see II.3.2). However, and adopting a conservative approach while awaiting confirmation of epidemiological findings, this value is maintained as hypothesis, and it must be emphasized that it should now be considered as rather pessimistic (notably in the context of a conservative calculation) and not be modified after reporting the 8th and 9th French cases of vCJD, even if these two latter cases are, for the first time, and consecutively linked to chance, also blood donors. It was predictable that blood donors would be found among the French population of subjects developing vCJD of dietary origin (see II.3.1).
As far as infectivity is concerned, the hypothesis was established that the blood of an infected individual is infectious throughout the incubation period and that it is not possible to specify the profile of variations over the course of time in infectious load (see III.5.2).
With regard to de-leukocytation, the hypothesis adopted is that this process does not result in total elimination of the infectious load initially present in blood obtained from a donor asymptomatic at the time of donation. The ability of leukoreduction to reduce potential infectious load of blood is still being studied, with contrasting results emerging (publications, without contradicting each other, are not in agreement concerning an efficacy value). The December 2000 report and its successive updates considered that leukoreduction may only contribute to reducing infectivity by acting on the infectivity fraction associated with cells, while recognizing that this measure is not in itself capable of totally eliminating infectivity.
Taking into account leukoreduction, despite this relative efficacy, remains valid. It is recommended to maintain this stage in the preparation of each LBP as well as plasma destined for fractionation. Although this stage does not totally eliminate infectivity, it cannot be ruled out that it contributes to its decrease and equally decreasing the possibility of transmission.

The special case of plasma, used as LBP (fresh-frozen plasma – FFP - and viro-attenuated plasma - VAP) was studied in the 2000 report, notably concerning the risk associated with "pooling" required for VAP and not found with FFP (one donor, one recipient). The conclusions, which in terms of risk analysis remain unchanged were: "*VAP, despite pooling, does not create any additional risk of vCJD in comparison with unity FFP*".

III.2 Blood-derived medicines

The principle of calculation of residual risk for BDM, as described in the 2000 report and its updates, remains valid. In particular, the experts confirm that it is legitimate to have adopted a very conservative approach for estimation of efficacy of preparation procedures in eliminating the vCJD agent. The strategy of adding together only stage reduction factors with a significantly different mechanism of elimination is valid. Overall, concerning calculations of the level of residual risk for each BDM obtained from plasma collected in France, the experts consider that:

- Initial hypotheses taken into account for calculation of residual risk, updated in February 2004, remain valid.

- Notifications of cases of vCJD in France and in the United Kingdom do not change hypotheses, in that they remain within the limits of estimations (see above). The frequency of contaminated (or contaminant) donations estimated at 1/120,000 (on the basis of estimation of the epidemic in the United Kingdom and of compared dietary exposure in France presumed to be 20 times less) remains essentially valid (see II.3). The second English transfusion case does not yet lead to consideration of the existence of an unknown but significant reservoir of asymptomatic carriers, which would require

upward revision of this figure (see II.3.2). Residual risk has been estimated using the hypothesis that BDM administered during 1 year of treatment were all derived from a given contaminated pool, while the frequency of one contaminated donation per 120,000 actually corresponds to a contaminated pool of about 5 to 8.

- The degree of infectivity of whole blood, considered to be 100 Inf-iv U/ml (December 2000 report) and adjusted to 20 Inf-iv U/ml (February 2004 update), takes into consideration the results of the most recent studies in animal experimental models. The same applies to the distribution of infectivity in plasma, which would seem to be 50% rather than 10%.

- Comparative effectiveness of the intravenous route as compared with the intracerebral route, presumed in 2000 to be 10 times less effective, is now considered to be equally effective.

In February 2004, residual risk of all BDM was increased by a factor of 10 in relation to starting hypotheses, more conservative than those of the 2000 report. Nonetheless, in view of the wide margin of uncertainty of estimation, this difference has no significant consequences. Furthermore, it is compensated for in the final calculation of residual risk by improvement in preparation procedures and their validations (see in Appendix 3 the table summarizing residual risk values calculated for each BDM, and contained in the February 2004 report).

III.3 Expression of degree of residual risk - interpretation

A degree of "residual risk" has been calculated for each BDM (see 2000 report and February 2004 re-update). However the question of interpretation of these values arises, notably when determining the degree of risk to which patients treated with different BDM had been exposed.
Calculation of risk for BDM leads to a residual value of infectivity which is considered to be present in the total amount of medicine concerned taken by a patient, during a period of 1 year, at the maximum dose. This value is always less than unity (e.g. 0.0035) and is expressed as a negative value by power of ten [3.5×10^{-3}] (which may also be given as a negative logarithmic value [-2.46 log]). As mentioned in the December 2000 report, there are two possible interpretations of this residual value and discussion of this subject has been reopened since the interpretation of "negative log" values depends upon hypotheses which can be created concerning the very nature of infectious load.
If it is accepted i) that infectious load is fractional and that it is distributed into sub-fractions, homogeneously in each of the vials of batches of finished products ; ii) that in order to be infectious, a minimum of one infectious unit must be present in the vial, and iii) that there is no cumulative effect of receiving amounts lower than the non-fractionated infectious dose, then a value less than an infectious unit (e.g. 3.5×10^{-3}, i.e. -2.46 log) would signify that the accumulation of infectious doses received in 1 year by a patient treated with the product considered would not be contaminant.
In contrast, in the hypothesis that infectious load is not fractional below 1 Inf-iv U, then a value of less than unity indicates that at least one infectious unit will be found, with the probability indicated by calculation, in one of the vials of the product. In other words, a value of 3.5×10^{-3} would indicate that among 35,000 vials, one vial is carrier of one infectious unit which will contaminate the person receiving that vial. This value hence expresses a given proportion of contaminated vials or a period at the end of which the patient would have received one contaminated dose.
In the current state of knowledge, it is difficult to prefer one interpretation rather than another. However studies of TSSE agents are suggestive of the concept of a non-fractional unit. This being the case, and by analogy with the concept of sterility in microbiology, the lower the residual value (near to 10^{-4} or even 10^{-6}) calculated for each BDM, the more the risk can be

considered to be negligible. For example, for an estimated residual risk of 10^{-4}, interpretation could be that probability for the patient taking the annual dose indicated in the calculation of receiving at most one vial containing one infectious unit, is 1/10,000.
By this interpretation, and taking into account residual risk calculations as updated in the February 2004 report, few BDM would then meet a "safety" threshold identical to that of sterility. However this interpretation of risk does not appear to be currently compatible with epidemiological and experimental data concerning BDM for which no case of transmission has been established. It must be remembered that hypotheses used for calculation of the degree of residual risk of each BDM are highly conservative, leading to probably overestimated residual values.

III.4 Estimated degree of risk should two donations from donors with vCJD contribute to preparation of a given batch of blood products

When calculating risk, it was considered in a worst scenario hypothesis, and despite estimation of a small number of expected cases of vCJD in the French population, that a contaminated donation would routinely be present in the plasma pool for fractionation. In view of the number of cases which might occur in France during the next 60 years (300 cases based upon a conservative approach), and aware of the proportion of blood donors in the general population, the probability of having simultaneously in the same plasma pool two donations from vCJD carriers is very slight. Nevertheless, even when retaining the hypothesis of two contaminated donations contributing to the same plasma pool for fractionation, calculation of residual risk shows that this would not modify the final result since the infectious load due to one donation is slight (20 Inf-iv U/ml). Hence two infectious donations in the same plasma pool would only multiply by two the total infectious load (i.e. 0.3 log of additional infectivity) at the start of the fractionation procedure.

III.5 Hierarchy of risk according to blood products

III.5.1 Transfusion products versus BDM

In view of the factors discussed above, the experts conclude that the degree of residual risk of transmission of vCJD by blood products is not affected in relation to estimations updated in February 2004.
It is possible to create a hierarchy of blood products according to their degree of risk so as to determine whether safety measures concerning these products are appropriate. The December 2000 report considered that LBP (including therapeutic plasma, fresh-frozen plasma or "viro-attenuated" plasma) had a higher degree of residual risk than BDM. Since calculations of residual risk remain valid, this hierarchy is retained. Furthermore, this hierarchy is confirmed by notification of cases now considered to be proof of transmission by transfusion, while no such case had been proven for BDM, and the fact that patients treated with BDM have a life expectancy far longer than transfused patients, though these findings do not enable quantification of risks.

III.5.2 Infectivity and interval of donation in relation to clinical phase

Notification of vCJD after donations in a blood donor raises the question of infectious load which might be present in various donations given throughout the incubation period. In other words, is a blood donation given 10 or 15 years before the clinical phase of the disease more, less or equally infectious as a donation given a few months before the onset of the first symptoms of disease? Such symptoms would then render the donor ineligible for donation. The

answer to this question affects the analysis of the risk of LBP received and of BDM manufactured, consumed and/or still in circulation.
A number of points were debated in this context:

- In terms of infectivity, the length of the incubation period of vCJD has not been definitively determined (as with other type of TSSE in humans), in that the precise date of contamination is most often unknown. Furthermore, it is known that the length of incubation depends upon several factors of host susceptibility, and in particular influence of host genotype according to the phenotype of the infectious agent. When first clinical symptomatology appears, it is very difficult, and above all for vCJD which is of dietary origin, to date contamination, i.e. the incubation period during which the individual was "at risk" even if a probability distribution at the time of contamination is available. Similarly, concerning the level of infectivity in blood or peripheral tissues during the incubation period, there are few available data on human TSSE. Experimental findings are not homogenous and consistent. They greatly depend upon the animal model studied (species and infecting strain). Overall, available data might suggest that the longer the donation precedes the onset of clinical symptomatology, the lower might be the level of infectivity. However it is not currently possible to determine a threshold in time beyond which donations could be considered as risk free.

- Blood products prepared from a plasma pool containing a donation identified as coming from a patient with vCJD differ from other blood products (here referred to as "all donations") by the fact that for the former, the entry of a contaminated donation in the manufacturing procedure is real and known, while for the latter, this remains at the level of the possible, but this has not been confirmed. It should nevertheless be pointed out again that this possibility has already been taken into account when calculating risk for BDM. This difference must be viewed in relative terms though emphasizing that it is possible that amongst "all donations", there might be at least one donation which subsequently proves to be from a donor with vCJD. This situation occurred in the United Kingdom starting in 1997 and has just been confirmed with the 8th and 9th French cases of vCJD.

As a result, on the basis of these factors, a classification of risks of exposure to infectivity could be suggested as follows:

- LBP obtained from donation of a donor with vCJD,
- LBP obtained from an "all donations",
- BDM obtained from a plasma pool incorporating a donation from a donor with vCJD,
- BDM obtained from an "all donations" (and possibly sub-categorized according to the cumulative total amount administered).

As explained above, it is however not possible to quantify in absolute terms the degrees of respective risks of these different categories.

III.5.3 Risk of blood products and dietary risk

Similarly it is not possible to estimate the degree of "additional" risk associated with the use of LBP or BDM, in comparison with the risk inherent to dietary exposure. It can only be stated that the use of blood products exposes to risk which is added to dietary risk, without it being possible to conclude that patients exposed to this iatrogenic risk are overall "more at risk" than the population as a whole. In the present state of knowledge, it is not possible to conclude whether individuals exposed to blood (by transfusion or by BDM) are a category of patients in whom

additional precautionary measures are required as compared with those already in place concerning exclusion of blood donation by certain "at risk" individuals, and whether stages of de-leukocytation of collected blood could or should be envisaged in order to decrease the risk of secondary transmission from these patients who are recipients of blood products. In the area of transfusion, a distinction could be made when it emerges that recipient patients have received blood from a donor who developed vCJD post-donation (see below for further discussion).

IV. EXPLOITATION OF THIS RE-UPDATE - POSSIBLE MEASURES TO BE PROPOSED

While the degree of risk of transmission of vCJD by blood and its constituents is not modified, the same does not apply to the perception of risk. The onset of two cases, deemed proven, of transmission by transfusion in the United Kingdom as well as the existence of two cases of vCJD in blood donors in France, shows that the risk of seeing in France transmission from transfusion, considered as a hypothesis in 2000 but which had not yet occurred, could actually concretely emerge in France. This modification of the perception of risk, while no new scientific finding has led to upward nor downward revision of the degree of risk, and the technical possibility of traceability in a real situation, naturally raise the question of the need or not for the creation of new measures in order to decrease the risk of "secondary transmission" (inter-human transmission) and consequently the need of informing patients who have already received various products, so that they comply with new health safety measures (and notably organ tissue or cell donation, and during surgical procedures).

IV.1 Need for monitoring

It is possible that a case of vCJD could be notified in an individual having received a blood product (LBP or BDM). It would then need to be determined whether this is the actual result of administration of the product or of dietary exposure (and surgical when applicable).
This raises the question of the need or not for particular monitoring of certain patients who have received LBP obtained from donors who later developed vCJD, as well as patients treated with BDM. Furthermore, in the latter population, it could even be envisaged that the approach should be different according to the type of BDM received, and cumulative total amounts (see above discussion on residual levels of infectivity in different BDM).
The experts have not yet given a definite answer to this question of the need for monitoring and follow-up. They suggest that consideration should be given in the general context of the monitoring of this type of pathology and the epidemic profile.
Among approaches investigated, the possibility has been raised of routine screening for pathological protein in autopsy specimens obtained following the death of hemophilia patients who would accept autopsy. The experts nevertheless feel that this prospective cohort would probably not give a fast and interpretable answer concerning the possibility of transmission by BDM. Various evaluations of the risk of prion transmission by BDM have all led to the conclusion of a very low level of risk (if a case of transmission occurred it would be a rare event). In view of the small number of hemophiliacs who could be monitored prospectively, a significant signal could be detected, if there is indeed a risk, only after many years of monitoring and the answer to the question raised as to the true nature of risk of transmission of CJD by a BDM could be provided by sources other than this prospective postmortem cohort.
The setting up of prospective studies and of specific monitoring therefore remains fully in question.

IV.2 Measures for exclusion from the donation of blood, organs, tissues and cells

Currently a history of transfusion is a criterion for exclusion from blood donation. This exclusion measure is hence pertinent in reducing the risk of secondary transmission by transfusion.
Additional measures of exclusion could possibly be envisaged, such as exclusion from the donation of organs, tissues and cells of patients who have received a transfusion and/or those treated with BDM. However the absolute value of risk of transmission of vCJD by blood or its constituents is not known, and there are no data providing objective evidence of the contribution of such measures to reduction of the risk of secondary transmission. It is hence necessary to first determine those blood products for which exposure to risk would justify the proposal of these exclusion measures. It would also be important to be aware of the impact of these exclusion measures on the availability (in view of the underlying context of penury) of donations of blood, organs, tissues and cells. These data could be taken into account in criteria used to decide whether to apply such measures intended to reduce the risk of secondary transmission.
Evaluation of different degrees of residual risk (see III.5.2) is a first approach to the hierarchy of blood products.

IV.3 Measures concerning care practices and surgical procedures

Circular No. DGS/5C/DHOS/E2/2001/138 of 14 March 2001 ("Circular 138"), defines precautions to be taken during care aimed at reducing risks of inter-human transmission of agents responsible for TSSE.

It has been confirmed to the experts that consideration is underway at the general health directorate to examine whether "Circular 138" should be updated in relation to the specific risk appearing to concern vCJD agent[2]. This circular is based at the outset on the hypothesis that the general population has been potentially exposed to dietary risk. The question is whether past administration of certain blood products is an identifiable risk factor, justifying taking specific measures and including these patients in one of the at-risk categories of the circular. The decision to classify certain persons exposed to a blood risk as "subject at individual risk", would lead to additional decontamination measures with considerable consequences concerning the management of medical and surgical equipment or invasive investigations (e.g. endoscopes).
In terms of the hierarchy of blood products regarding the risk of transmission of a TSSE agent, it would need to be determined whether recipients enter current categories of the circular or whether some should be identified specifically in a category requiring enhanced measures concerning medical and surgical equipment, e.g. patients transfused with an LBP obtained from donation of a donor with vCJD.

Another criterion is the concept of an at-risk procedure, where particular attention must be paid to procedures which are currently insufficiently codified, notably in dentistry, with determination as to what extent these procedures could be responsible for (or contribute to) recirculation of the pathogenic agent (secondary transmission).

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2 - The 14 March 2001 version of Circular 138, regarding practices related to care (and in particular dealing with medical devices after an invasive procedure), draws a distinction between:
- categories of patients:
* without any particular characteristics,
* at individual risk,
* suspect or affected,
- categories of at-risk procedures in relation to at-risk tissues and in particular:
* central nervous system, eye and optic nerve,
* lymphoid structures.

IV.4 Comparative efficacy of exclusion methods and measures concerning care practices and surgical procedures

As soon as measures for exclusion from blood, organ, tissue and cell donations might be taken against certain patients who are recipients of blood products (LBP and BDM), evaluation would be required of their impact on the expected benefit of other measures which might also be initiated, later, concerning care practices and surgical procedures such as measures for the decontamination or use of disposable equipment.
The respective contribution of these different measures in decreasing risk of "secondary transmission" must be evaluated. However the experts consider that it is not possible to comment on the comparative efficacy of these two areas of measures nor is it possible in the present state of knowledge to comment on the appropriateness of whether or not they should be associated.

IV.5 General recommendations expressed in 2000

Apart from possible new measures which might be proposed in order to further minimize the risk of transmission by blood products, and the risk of secondary transmission by individuals recognized subsequently as having been exposed to this risk, the experts expressed their wish for retention of those general measures, stated as early as 2000, and notably those concerning strict limitation of the number of individuals exposed to products derived from the human body and more specifically blood products (and especially the use of transfusion products).
This limitation of the exposed population concerns in particular strict compliance with indications for the use of blood products so that they should be used whenever benefit greatly outweighs potential risk.
These guidelines should be redistributed.

APPENDIX 1

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APPENDIX 2

Calculation used by British health care authorities to identify the risk of exposure to vCJD agent by blood-derived medicine (BDM) - Comparison with French experts' group evaluation

For their estimation of the risk of transmission of vCJD by BDM, British authorities have used various evaluation factors brought together in a report prepared by the consulting company Det Norske Veritas Consulting (DNV) and updated in 2003 (www.dnv.com/consulting/news_consulting/RiskofInfectioufromvariantCJDinBlood.asp).
On the basis of these quantitative evaluations, the British authorities adopted, with a conservative and deliberately maximalist approach, several working hypotheses in order to quantify the residual risk of infectivity in BDM.

This appendix briefly reports hypotheses and calculation methods adopted by British authorities, which are then compared with the French experts' group approach.

REVIEW OF CALCULATION HYPOTHESIS ADOPTED BY BRITISH HEALTH CARE AUTHORITIES

Accumulation of infectivity, and definition of a "significant" threshold beyond which an individual is considered to be "at risk"

Whenever an individual is exposed to material of human origin (e.g. blood donation), when the donor is subsequently diagnosed as carrying Creutzfeldt-Jakob disease, and in particular here the variant of the disease (vCJD), it must be considered that the individual has been exposed to infectious material. It is then possible to calculate a total cumulative dose of exposure to the infecting agent for a given individual, according to the type of product received, dose and route of administration. This situation of a "cumulative" risk implies, according to the DNV report (see in particular Appendix II, "probabilistic" model and "threshold dose" model, p. II-44), that any infectious unit or fraction of an infectious unit present in a product administered is "captured" by the individual, that it is not eliminated, and that any further administration of an "at risk" product accumulates infectivity of the previous dose, regardless of the time elapsed between the two exposures. It is accumulation of these "fractions of infectious doses" which results in reaching and exceeding the threshold considered to be "significantly infectant".

Determination of limit threshold of infectivity: 0.02 infectious units, expressed as ID_{50}

The limit threshold of infectivity is fixed as the cumulative dose of "0.02 ID_{50} of infectious units[3]" which an individual would have received over a given period of exposure.
This cumulative dose, chosen on the basis of a model of transmission of infectivity by release from reused surgical instruments, corresponds with the possibility of having been exposed at a risk of 1% or more of infection, in comparison with the general risk, of dietary origin to which all of the population of the United Kingdom has been exposed.

3 - Infectivity can be expressed either as "infectious dose 50% (ID_{50}) which is the dose infecting 50% of individuals exposed to this dose, or as infectious units (InfU) corresponding to the minimum amount such that an individual would be infected with a probability of 100%. It can broadly be accepted that 2 ID_{50} = 1 InfU.

Calculation of infectivity for blood-derived medicines

Working hypotheses

On the basis of infectivity hypotheses suggested in the DNV report (see details in Appendix II of DNV report), the British authorities calculated residual infectivity which could be present in each type of BDM (clotting factors, immunoglobulins, albumin, etc.)
This calculation considers that infectivity, present in donor blood, is distributed throughout the stages from whole blood to plasma for fractionation, then the fractionation procedure until finished product. Such distribution leads to residual infectivity in different products, which depends upon their degree of fractionation in relation to blood and initial plasma. No other factor for the reduction of infectivity is taken into account, and notably the ability of various fractionation stages to eliminate the agent, by partition or retention.
In brief, the calculation can be summarized as below (see p. 14 of DNV report and Appendices I and II):

1. One blood donation from a donor incubating vCJD provides 900 infectious units expressed as ID_{50} (in a volume of 450 ml).

2. Whole blood is separated into three first constituents:
   - red cells, containing 219 ID_{50},
   - packed white cells (and platelets) where there are 201 ID_{50},
   - plasma (225 ml) containing 480 ID_{50}.

3. Starting from plasma, basic fractions can be separated for the preparation of BDM. In each fraction (starting from a volume of 225 ml of plasma), total infectivity is distributed as follows:
   - cryoprecipitate 60 ID_{50} (from which factor VIII is derived in particular),
   - fraction I+III: 34.4 ID_{50} (for production of immunoglobulins),
   - fraction II: 1.6 ID_{50},
   - fraction IV: 11.5 ID_{50},
   - fraction V: 3.4 ID_{50} (for production of albumin).

4. Calculation of the degree of infectivity of a BDM obtained from a plasma pool containing one or more donation(s) from donor(s) who subsequently developed post-donation vCJD, then requires the following to be taken into account:
   - the number of infected donation(s) in the plasma pool,
   - extraction yield from plasma to produce BDM,
   - the total amount of BDM concerned, produced from the initial plasma pool.

Numerical application - Calculation for a preparation of factor VIII (FVIII)

By way of a numerical application for a product of FVIII, and using mean production data (yield, volume of initial pool) as presented in Appendix II of the DNV report, it can be considered that:
- a plasma pool containing a donation from a donor subsequently developing vCJD, i.e. an initial infectious load of 900 ID_{50},
- preparation of FVIII from cryoprecipitate, i.e. infectious load of 60 ID_{50},
- based upon the mass of cryoprecipitate obtained from a plasma pool, about 900,000 international units (IU) of FVIII can be derived (in view of extraction and purification yields, see p. II-32 in the DNV report),
- 60 ID_{50} are hence distributed between the 900,000 IU of FVIII, i.e. an infectivity of 60 ID_{50}/900,000 IU = 6.7×10^{-5} ID_{50} per IU of FVIII,

- in a patient treated with FVIII from this batch, it suffices to receive $0.02/6.7\times10^{-5}$ = 298 IU of FVIII in order to reach the infectious threshold dose of 0.02 ID_{50}.

On the basis of this very conservative calculation, the British authorities considered that all hemophiliacs who had received clotting factors derived from cryoprecipitates obtained from English plasma collected in the United Kingdom in the years 1980-1997 were "at risk" (eight British donors have developed post-donation vCJD, plasmas from them having been incorporated in 23 plasma pools used to produce BDM between 1980 and 1997).

COMPARISON WITH FRENCH METHOD OF CALCULATION

French experts have adopted a considerably different calculation approach. They suggest the calculation of residual risk, in a given patient, of exposure to infectivity per year of treatment, with the BDM concerned and at a fixed annual dose.
In short, it has been considered in the calculation (see details of calculations in December 2000 report and values adopted for calculation as modified in the February 2004 update):

- that each plasma pool from which BDM are produced contained one donation from a donor incubating vCJD and that the blood of this donor carried infectivity of 20 infectious units (InfU) per milliliter of plasma,
- the plasma contains 50% infectivity. Plasma from the incubating donor therefore provides (per 280 ml of plasma per blood donation) 2800 InfU which are distributed in the plasma pool,
- an extraction yield for each type of BDM (e.g. for FVIII a yield of approximately 100 IU of FVIII per liter of plasma may be considered - the DNV reported yields of 200 to 150 according to the purity of FVIII, p. II-32) and taking a total volume of 6000 liters of plasma pool, this leads to infectivity of 4.7×10^{-3} InfU per IU of FVIII[4],
- a global reduction factor (RF) contributed by the procedure (here in the case of FVIII an RF of 6 logs can be considered, taking into account only those stages which have been duly validated for their ability to eliminate the agent). Residual infectivity of one IU of FVIII is therefore then 4.7×10^{-9} InfU per IU of FVIII,
- at a maximum annual dose (e.g. for FVIII, a dose of 500,000 IU has been adopted).

On the basis of these hypotheses, in an individual treated for 1 year with a total of 500,000 IU of FVIII, residual risk is 9.7×10^{-4} InfU, i.e. as decimal log "-3.01 $\log_{10}$".

Interpretation of this residual risk value, adopting the interpretation of British health care authorities, would be that after 1 year of treatment with LFB (French Laboratory for Fractionation and Biotechnology) FVIII (rounded off to the nearest figure and without taking into account the mode of expression of infectivity), a hemophilia patient does not reach the "limit threshold of infectivity" fixed at 0.02 ID_{50}.

4 - It is noted that with residual infectivity associated with each international unit of FVIII depends upon extraction yield (and hence the purity of the product) as well as the volume of the plasma pool initially used.

APPENDIX 3

Degree of residual risk updated in February 2004 for BDM made available in France by the LFB

	Residual risk (IU) as $\log_{10}$
Factor VIII	-3.21
Factor VII	-1.65
Factor IX	-5.51
Factor XI	-3.04
von Willebrand factor	-7.18
Fibrinogen	-3.63
PPSB	-3.57
Antithrombin III	-1.43
C protein	-4.85
Albumin 4%	-3.25
Albumin 20%	-3.55
Alpha 1 antitrypsin	-4.81
Polyvalent Ig	-6.03
IV anti-B Ig	-2.97
IM anti-B Ig	-7.46
Anti-D Ig	-5.79
Antitetanus Ig	-7.58