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# Risk of transmission of Creutzfeldt-Jakob disease via blood and blood products. The French risk-analysis over the last 15 years

## *Risque de transmission de la maladie de Creutzfeldt-Jakob par le sang et ses dérivés. L'analyse de risque française au cours des 15 dernières années*

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**Abstract**

Risk of transmission of Creutzfeldt-Jakob disease (infectious agent, responsible of spongiform encephalopathy) via blood and blood components (including the plasma-derived medicinal products such as coagulation factors and immunoglobulins) have been a subject of concern for Health authorities since the early 1980s, with a regain of interest in the 1990s, with the bovine spongiform encephalopathy outbreak followed few years after with the notification of the first cases of variant Creutzfeldt-Jakob disease in humans. The risk-analysis and measures taken by the French authorities in the period 1990–2010 will be described with the various assumptions and working hypothesis used and revisited as new findings become available.


*Keywords:* Creutzfeldt-Jakob disease; Transmissible spongiform encephalopathy; Risk analysis; Transfusion-related risk; Plasma-derived medicinal products

**Résumé**

Le risque de transmission de la maladie de Creutzfeldt-Jakob (agent infectieux transmissible, responsable d'encéphalopathie spongiforme), par le sang et les produits dérivés du sang (notamment les médicaments dérivés du plasma, tels que les facteurs de la coagulation ou les immunoglobulines) a été au centre des préoccupations des autorités sanitaires dès les années 1980s, avec un regain d'intérêt dans les années 1990 avec l'apparition d'une part de l'épidémie de « vaches folles » en Angleterre et les premiers cas variants de la maladie de Creutzfeldt-Jakob en 1996. L'analyse de risque conduite par les autorités françaises tout au long de la période 1990–2010 est rappelée, avec les hypothèses de travail qui ont été utilisées et révisées au fur et à mesure des nouvelles données expérimentales et nouvelles notifications de cas.


*Mots clés :* Maladie de Creutzfeldt-Jakob ; Encéphalopathie spongiforme transmissible ; Analyse de risque ; Risque transfusionnel ; Médicaments dérivés du sang

## 1. Introduction, background

This presentation is aimed at summarising the risk-analysis made by the French competent authorities as regards the risk of transmission of spongiform encephalopathy agent, responsible for the Creutzfeldt-Jakob disease (CJD) in human, via blood and blood components, including plasma-derived medicinal products. The assumptions and other quantitative parameters used in the calculations made by the ad hoc expert group will be explained as well as the context of uncertainties in which the various concerns have progressively emerged with this agent.

A brief introduction to present the transmissible infectious agent and to remind that the knowledge on this agent, its precise nature and tissular distribution was very limited at the start of the bovine spongiform encephalopathy [BSE] (the so-called "mad cow disease") outbreak in the UK in the 1980s. The limited knowledge on CJD was on the sporadic (sCJD), familial (fCJD) and iatrogenic (iCJD) forms of the disease in human. At the same time in the animal realm, this was the scrapie disease, affecting sheep, which was considered as the lead disease with

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no spontaneous/natural cases reported in other animal (mammal) species. Knowledge has then improved at an accelerated pace, while some first precautionary measures, taken in a large context of uncertainties, had to be considered so as to limit the risk of transmission from animal to human or inter-human.

The agent, responsible for transmissible spongiform encephalopathy (TSE), is called "prion" or PrPres. It is an abnormal form of the natural protein PrP, expressed in mammal species [1,2].

Prion is of proteinaceous nature (it has so far not been possible to identify any genetic material attached to the protein), highly resistant to inactivating agent (including high temperatures or oxidative agents) and highly hydrophobic, capable to stick to a large variety of materials and surfaces, so that the risk of cross-contamination via material, which could have been in contact with tissues (particularly those associated with central nervous system) from diseased person, was considered high.

The tissular distribution, for scrapie and sCJD in infected organisms (i.e. in animals or human beings incubating the disease or having clinical symptoms) was initially claimed to be restricted to the central nervous system. However, with the first cases of variant CJD (vCJD) published in 1996 [3] as the result of a human contamination with the BSE form of the prion, by the food chain, a more peripheral distribution should also be considered and particularly in the lymphoreticular formations [4]. Infectivity, at that time was also described in blood and blood components (particularly the plasma and the buffy coat) of animals (mice, rat, hamster) experimentally infected with BSE, Scrapie or CJD strains [5].

## 2. Situation in France before 2000

One can divide into two periods the French handling of the TSE-risk in health products, including blood/blood components for transfusion and medicinal products derived from human fluids (i.e. plasma and urine), with November 1996 as the cutting date when the first cases of vCJD were described in patients, confirming the hypothesis that an infectious agent had crossed the species barrier and was now adapted to human with all the possible risks of inter-human transmission by any route of contamination.

### 2.1. Before November 1996

Up to 1996, the risk of transmission of sCJD from human to human was considered remote, if not theoretical. Some epidemiological data (although on small numbers of cases) were available, indicating a very stable annual incidence of sCJD in countries with valid epidemio-surveillance system in place [6]. The iatrogenic cases of transmission were all due to either neurosurgical procedures (cornea or dura-mater graft, brain electrodes) or administration of medicinal products extracted from brain tissues such as pituitary derived hormones (hGH, FSH or LH) [7]. All iatrogenic cases were coherent with a contamination stemming from a contact with brain tissues from infected (and not diagnosed) patients or deceased donors. Therefore, by 1994 in France the measures in place to minimise the risk of transmission concerned essentially blood donation with deferral of blood donor at risk of developing CJD, i.e. any subject:

- having a family history of CJD;
- who had received a corneal or dura mater graft;
- who had been treated with medicinal products derived from human pituitary glands, or who had history of serious CNS diseases.

It is noteworthy that these criteria have later (2004) been laid down in the Commission Directive on blood donation (Dir. 2004/33/EC). France took also additional measures, such as a permanent deferral from donation for subjects previously transfused, and implementation of a recall policy for batches of plasma-derived medicinal products produced from a plasma pool having incorporated a donation from a donor who later developed sCJD.

### 2.2. After November 1996

In 1996, as explained above, a new form of CJD was detected in four UK patients (young patients as compared to the median age for sCJD), who all had been exposed via the food chain to bovine materials sourced in the UK, during the BSE epidemic [3]. This new clinical form of CJD, qualified at that time, as a "variant" of the disease (vCJD), has raised alarm and concerns insofar as the agent was differing clearly from the sporadic profile and considered as a human adaptation of the bovine pathogenic agent initially transmitted by oral route.

As it was a new disease identified, no epidemiological data were available and very little, if nothing, was known about this new "adapted" agent and to what extent the adaptation had modified the overall behavior of the agent, acknowledging as a first evidence of a variant form, the specific clinical symptoms. It was thus prudent to consider, at that time point, some more precautionary measures, particularly for blood and other human-tissue derived materials.

An ad hoc group of experts was set up in 1996 to discuss the various issues raised and to build up an as exhaustive as possible knowledge database on the agent, the physiopathology and risk of transmission, so as to provide enough material for risk assessment and decision-making process. There was indeed a great concern on the possible risk of human transmission and recirculation of this agent via blood or blood-derived products.

However, despite the first cases of vCJD, no other measures have been deemed necessary, and particularly, not to interrupt in contrast with the UK decision, the French plasma fractionation (to derive mainly the immunoglobulins and coagulation factors, for which there was no or few alternatives). Also, no exclusion criteria had been decided for donors who spent time in the UK during the BSE outbreak.

## 3. The first extensive risk analysis performed in 2000

The first risk analysis has started during 2000 when more information became available, and additional concerns arose with the first results published by Houston et al. [8] and showing