PRIONS & BIOSAFETY

SAFE LABORATORY MANAGEMENT OF PRIONS IN FRANCE

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INVESTIGATE, EVALUATE, PROTECT

18/10/2022

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SAFE LABORATORY MANAGEMENT OF PRIONS IN FRANCE

1. Prion risk

- Infectious agent in prion disease
- Risk Analysis of Prion
- Occurrence and transmission

2. Assessment of "safety control plans" across prion research laboratories

Mission of security expertise in infectious prion research laboratories

IGÉSR 2020-123/CGAAER n° 19081 - september 2020

Second mission of security expertise in infectious prion research laboratories

IGÉSR 2022-011 / CGAAER n° 21101 – january 2022

External audits

Directors General of Agencies

3. Safe laboratory management of Prions in the wake of recent events

- General regulatory framework
- Prion regulatory framework
- Prion "Good practice guide »

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Safe laboratory management of prions in France

1. Prion risk

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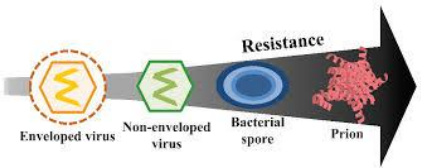
1— Prion risk infectious agent in prion disease

Features

- Progressive neurodegenerative disorders,
- Always fatal,
- Long incubation periods,
- **Cross-species transmissible**,
- Lack of treatment,
- Misfolded and aggregated prion proteins.

Aggregated proteinacious material

- **Incredibly resilient to degradation**,
- Disinfectant procedures used for viral, bacterial, and fungal pathogens are either ineffective or variably effective,
- *In vitro* studies have demonstrated that disrupting large aggregates into smaller aggregates increases cytotoxicity,



Sakudo, A et al. Recent Advances in Prion Inactivation by Plasma Sterilizer. Int. J. Mol. Sci. 2022, 23, 10241

Experimentally transmissible …

Oral route, corneal, intraperitoneal, intravenous, intranasally, intramuscular, intra-linguale, subcutaneous or **intracerebral**. **The most efficient route of infection is direct intracerebral injection**.

Aerosol transmission of prion was confirmed in mice, but with **massive exposure** (mouse infectious brain grind).

In humans, some routes of transmission are demonstrated …

By **transfusion** of blood products from v-CJD patient: 3 clinical cases of v-CJD and 1 asymptomatic case (blood transfusion with red cells that had not been leucodepleted).

By **grafting dura mater** or **cornea** from an infected donor.

By administration of **growth hormone**.

Feeding: Kuru by ingestion of the brains of contaminated cadavers and BSE by ingestion of bovine products (emergence of v-CJD).

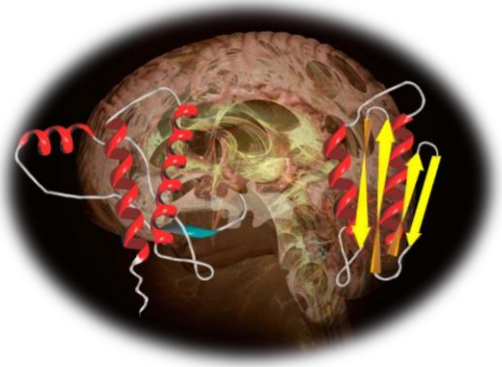
In humans, some routes of transmission seems plausible…

Reusable medical devices during invasive procedures :

- Central nervous system, retina and optic nerve, spinal and trigeminal nodes, olfactory mucosa,
- Only for v-CJD, organized lymphoid formation.

What Determines Transmissibility ?

Factors affecting transmission during accidental exposure…



- Variation in the individual strains
- Individual risk factor (age, genetic)
- Species barriers
- Variable degrees of infectivity
- Modes of spread

1— Prion risk Occurrence and Transmission

Public data : *reference body for occupational risk prevention (France : INRS)*

No evidence suggesting the transmission of TSE in occupational environments,
Sources of exposure risk are known for:

- Health-care personnel,
- Farmers,
- Veterinary surgeons,
- Slaughter house operators.

1— Prion risk Occurrence and Transmission

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Published data : *case-control studies*

No increased risk for health professionals

Van Duijn et al., 1998

Observation: 1993–1995 (France, Germany, Italy, Netherlands, United Kingdom)

405 cases, 405 controls (hospital-based)

No significantly increased risk for health professionals

Wientjens et al., 1996

Observation: 1975–1984 (Japan, United Kingdom, United States),

178 cases, 333 controls (hospital based, community based, and spouses)

Ruegger et al., 2009

Observation: 2001–2004 (Switzerland)

69 cases, 224 controls (from general practitioners and random digit telephone dialing)

Increased risk for health professionals/physicians

Cocco et al., 2003

Observation: 1984–1995 (United States)

636 cases, 3,180 controls (population-based from a death registry)

Increase case reported over time for physicians

Hermann et al., 2020

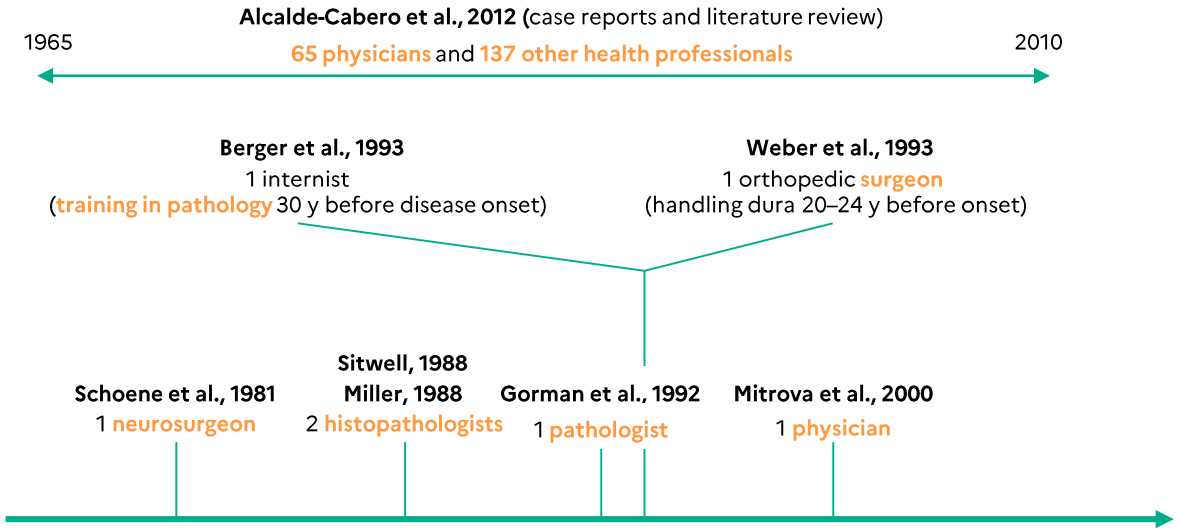
Observation: 1993–2018 (Germany)

17 physicians, 1,515 suspected cases of human Prion disease

1— Prion risk Occurrence and Transmission

anses

Published data : *case reports*



! Debatable !

- Lack of formal evidence of occupational origin.
- Ages compatible with «sporadic» CJD.

Research laboratories… 3 cases where an accidental cause must be considered.

2016 - Italian patient with v-CJD, having worked in a Prion laboratory.

- **Manipulation** of brain samples infected with **BSE** and **v-CJD**,
- Investigation **did not disclose a laboratory accident**.

Research laboratories… 3 cases where an accidental cause must be considered.

2019 - Death of a 33-year-old researcher of prion diseases from v-CJD.

9 years after a percutaneous exposure to prion-contaminated material :

*- Handled frozen sections of brain (**human tg mice** overexpressing PrP with methionine at codon 129),*

*- Mice had been infected with a **sheep-adapted form of BSE**,*

*- **Stabbed her thumb** through a double pair of latex gloves with the sharp ends of a curved forceps used to handle the samples.*

- Researchers cannot entirely rule out the possibility that the patient developed v-CJD after eating contaminated meat,

*- The **hypothesis of accidental transmission emerged**…*

→ «If we consider that this case is accidental, we can only be **very surprised** at the possibility of transmission **so fast by a simple sting**. Indeed, it was not a big wound with a scalpel that would have been used to cut off the brain. It was only **a round trip with a small tip**. Nor was it a hollow syringe needle containing brain tissue»
Dr Stéphane Haïk *(Coordinator of the National Reference Centre for Non-Conventional Transmissible Agents)*.

Research laboratories… 3 cases where an accidental cause must be considered.

2021 – In june, a 67-year-old patient was diagnosed with v-CJD or "classic" CJD.

- *Having worked in a Prion research laboratory,*
- ***No knowledge of laboratory accident****.*

Research pause in France: **moratorium on Prion research**

july 2021

"The suspension period put in place … will make it possible to study ***the possibility of a link*** *between the observed case and the person's former professional activity and to* ***adapt****, if necessary, the* ***preventive measures*** *in force in the research laboratories,"*

Prions & Biosafety

Safe laboratory management of prions in France

2. Assessment of “safety control plans” across prion research laboratories

2— Assessment of "safety control plans" across prion research laboratories Mission of security expertise

Mission of security expertise in infectious prion research laboratories

IGÉSR 2020-123/CGAAER n° 19081 - *september 2020*

Why ?

June 2019 - death of a 33-year-old researcher of prion diseases from v-CJD.

Who ?

- Minister of Higher Education, Research and Innovation,
- Minister of Agriculture and Food.

Aim ?

Assess the quality and completeness of "***safety control plans***" across prion research laboratories.

General observations :

- **Complex regulatory framework** leading to a fine and adapted risk assessment,
- **Scientific uncertainties** about the conditions of prevention and safety,
- **Low accident rates** but the need to move towards zero accidents given the possibility of transmission and lack of treatment.

***17 other lab accidents involving prions** in the past decade, five of which involved cuts or stabs*

2— Assessment of "safety control plans" across prion research laboratories Mission of security expertise

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Field observations : Overall **regulatory compliance** but likely to be improved

Overall **compliance of premises and equipment**

Vigilance of the teams on the **decontamination processes** but weak framework

Satisfactory management of **prion-contaminated waste** but traceability needs to be enhanced

Staff support does not take into account the **specificities** of the **Prion risk** (professional medical follow-up, training of staff insufficiently formalised)

Lack of harmonised practices

2— Assessment of "safety control plans" across prion research laboratories Mission of security expertise

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IGÉSR 2020-123/CGAAER n° 19081 - *september 2020*

Recommandations :

- Identify/organize an **interdepartmental framework** for monitoring safety issues : prions and possibly prion-like,
- **Enhanced the control** of Prions or Prion-like research activities through ministerial instruction,

- Create post-exposure and post-occupational regulatory **monitoring for prion-exposed agents,**

- Produce **guide to good practice** to Harmonize preventive and safety measures,
- **Initiate a program** about modalities of contamination and appropriate prophylactic measures (prions and prion-like),

- Extend the missions of **National Reference Centre** for Non-Conventional Transmissible Agents to expertise in **safety and prevention** of accidental occupational contamination.

2— Assessment of "safety control plans" across prion research laboratories Second mission of security expertise

Second mission of security expertise in infectious prion research laboratories

IGÉSR 2022-011 / CGAAER n° 21101 – january 2022

Why ?

- June 2021 - A 67-year-old patient diagnosed with v-CJD or "classic" CJD
- Research pause in France

Who ?

- General Inspection of Education, Sport and Research,
- General Council of Food, Agriculture and Rural Areas.

Aim ?

- **Investigate** the patient's case,
- Defined **recommendations** for lifting the moratorium.

Conclusions of the expert mission :

- **High probability** of contamination following a **cut with a microtome blade** «probably contaminated by tissues positive for **BSE** " in April 2005 (patient died of v-CJD, november 2021).

- Investigators have not ruled out the possibility **of another route of contamination**:

"**Airborne contamination**, which seemed extremely unlikely 30 years ago, has probably **become possible** because of the high concentration of prions obtained in the laboratory, coupled with the use of techniques that generate aerosols".

2— Assessment of "safety control plans" across prion research laboratories Second mission of security expertise

Second mission of security expertise in infectious prion research laboratories

IGÉSR 2022-011 / CGAAER n° 21101 – january 2022

Recommandations of the expert mission :

- Create a "**committee**" to address Prions security nationally,
- Ensure the **independence of laboratory security managers** from their management to avoid interference,

- Enhance the **traceability** of staff exposures and improve the **training** and **information**,

- Product a **Good practice guide** to update and harmonise safety procedures,
- Implement **external audits** prior to the resumption of the research activities,

- Explore the opportunity to extend priority safety measures to **prion-like research**.

2— Assessment of "safety control plans" across prion research laboratories External audits

Why ?

End moratorium : apply the recommandation of the "second mission of security expertise".

Who ?

Directors General of Agencies concerned.

Aim ?

Verification that laboratories have established and implemented the **organizational and technical arrangements** according to "**Good practice guide**".

External audits composition: multi-institutional audit teams

- Expert responsible for occupational safety
- Microorganisms and toxins expert
- Prion expert

Only "**Prion scientific expertise**" must absolutely be **external**, in any case have no direct link with the unit concerned.

2— Assessment of "safety control plans" across prion research laboratories External audits

Audits process flow :

1- Carrying out **on-site audits** : identification of strong points/deviations/non-conformities on the **basis of the "Good practice guide"**,

2- Auditors transmit a preliminary report,

3- Correction of the preliminary report (report errors or need for clarification),

4- Submission of a final report,

5- The **Director-General** convenes the "Committee of Health, Safety and Working Conditions" for an opinion on the resumption of activity and **decides** on the resumption or not.

Gradual resumption of research activities

anses **January 26, 2022**

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3— Safe laboratory management of Prions in the wake of recent events General regulatory framework

Protective measures about pathogenic biological agents classified 2 to 4

Technical preventive measures *(Order of 13 August 1996)*

Measures of confinement *(Order of 16/07/2007)*

Rules of good practice *(Order of 23 January 2013)*

Labour regulations – protection of workers

French labour code *(Order 94–352 du 4/03/1994)*

European directive *(200/54/CE du 18/09/2000)*

3— Safe laboratory management of Prions in the wake of recent events Prion regulatory framework

anses

Prion regulations

Precautions to be observed to **reduce the risks of non-conventional transmissible agents** *(Circular of 14/03/2001)*

Updating of recommendations to reduce the risk of transmission of non-conventional transmissible agents **during invasive acts** *(DGS/RI3/2011/449 of 1 December 2011)*

Prion regulations

Screening laboratories

Technical Instruction establishing the **requirements to maintain accreditation for TSE screening** *(Since 2002, Directorate General of Food : DGAL/ French Veterinary Services)*

Updated in September 2022 :

- Recommendations concerning the **management of liquid waste and effluent** at risk Prions.

- Possibility to **derogate** from the rule on **premises dedicated to the Prions**(requirements regarding staff, work organisation or decontamination and inactivation procedures)

- Clarify the procedures for requesting the **reassignment of premises** during a **cessation of activity** (provision of a framework describing the procedure to be followed)

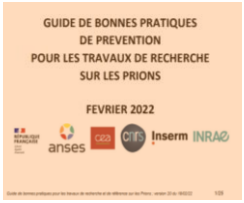
3— Safe laboratory management of Prions in the wake of recent events

Prion regulatory framework

Prion regulations

Infectious prion research laboratories

"Good practice guide" (drawn up *by the different research institutes working on prions, February 18, 2022)*



Review of the fundamental principles

- **Risk reduction** and **assessment**,
- Modalities of **contamination** of Prion,
- **Classification** of Prion in research.

Technical provisions to be complied with

- **Safety organisation** :
  Containment zone referent,
  Security assessment of research protocols.

- Organization in case of **emergency or accident** :
  First Aid Worker training,
  Instructions in case of accident on person,
  Accidental tipping of infectious biological material.

- Support of the **staff** :
  Traceability and medical surveillance,
  Training

3— Safe laboratory management of Prions in the wake of recent events

Prion regulatory framework

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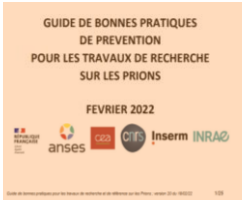

Review of the fundamental principles

- **Risk reduction** and **assessment**,
- Modalities of **contamination** of Prion,
- **Classification** of Prion in research.

Technical provisions to be complied with

- The requirements for the **premises** :
  - Design rules,
  - Dedicated to the Prions,
  - Qualification and maintenance expectations,
  - Cleaning, treatment of waste and effluent.
- Standard **personal protective** equipment.
- Laboratory **equipment** :
  - Dedicated to the Prions,
  - Single-use,
  - Avoiding the use of sharps.

Securing the main contamination

*Main routes of contamination are the **skin** route, the **ocular** or **oral mucous membranes***

***Cut, stitch,** carry or projection*

Minimize aerosol formation

*Choose the **technical process***

*Use the most suitable **equipment***

Minimize contamination

*Respect the **lockdown** rules*

***Monitor critical** premises, equipment and materials*

*Decide on rules for the **release** of equipments and laboratories*

Learning and understanding …

***Access** to the laboratory*

***Personal protective equipment** instructions*

*Pathogen **inactivation** protocols and waste management*

***Safety instructions** (incident, accident)*

Thank you for your attention

« An ounce of prevention is worth a pound of cure »