



# Surface contamination with 5-fluorouracil in 30 French hospitals of the Rhône-Alpes region

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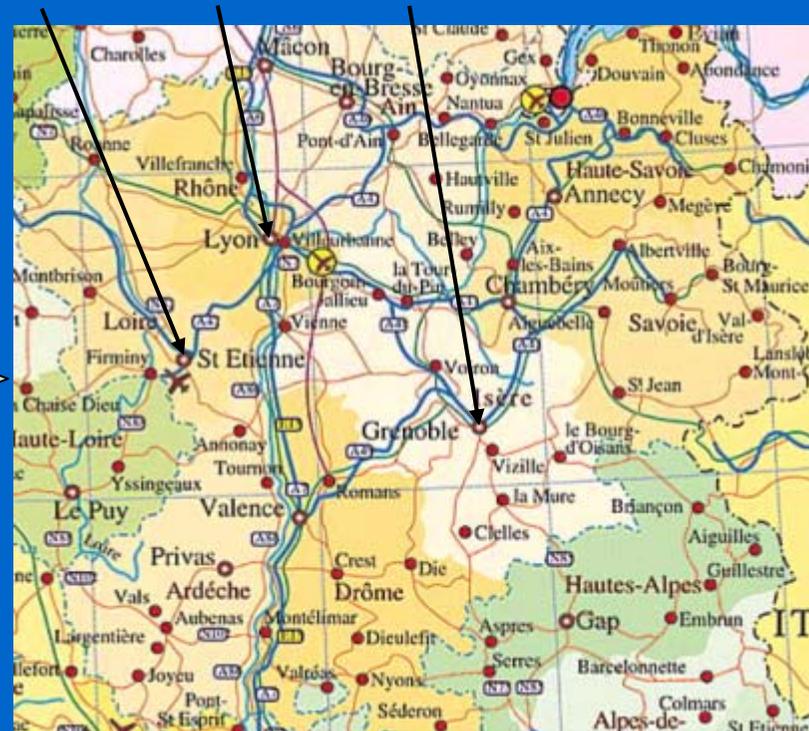


# Plan

- I. Context
- II. Rhône-Alpes 2006-2007 study
- III. French regulations
- IV. Limits and future prospects

# I. Context

- The Rhône-Alpes region: 44 000 km<sup>2</sup>, 6 million inhabitants
  - 3 teaching hospitals: Saint Etienne, Lyon and Grenoble



- 1 cancer treatment centre: Lyon



# I. Context

- The Centre Léon Bérard (Lyon) is the cancer treatment centre of the Rhône-Alpes region:

Preparations of cytotoxic drugs:

- 1996: **21 000**
- 2007: **44 000**

- **ONCORA** is the cancer network of the Rhône-Alpes region:

- 40 hospitals
- Main objective: collaborative implementation of clinical guidelines
- Group of pharmacists : harmonization of chemotherapy regimens, improvement of standard operating procedures during cytotoxic drug preparation, preliminary studies for the « contamination laboratory »
- 2003: creation of a specialised laboratory aimed at evaluating environmental contamination by cytotoxic drugs in hospitals
  - \* Initial funding: Regional Health Administration (ARH)
  - \* Objective: self-financing of the laboratory



## I. Context: Scientific background

- **Environmental contamination:**
  - T Connor's and/or P Sessink's studies
  - Contacts with R Schierl and T Kiffmeyer
  
- **Improvement of preparation techniques:**
  - BR Harrison's study using fluorescein as training material (AJHSP 1996)
  - Use of closed-system drug transfer devices



## I. Context: Preliminary study

- **Objective:** to determine the level of contamination with 5-fluorouracil (5FU) of different cytotoxic drug preparation units
- **Study design:**
  - 6 hospital pharmacies: 3 using Biological Safety Cabinets (BSCs) and 3 using isolators
  - Between 3 500 and 26 500 preparations per year
- **Method:** wipe sampling on several surfaces within and outside BSCs and isolators
- **Results:** measurable amounts of 5FU detected:
  - In **79.2%** (19/24) of the surface samples within isolators (**8.3%** within BSCs: 1/12)
  - In **29.6%** (8/27) of the surface samples outside isolators (**no positive samples** outside BSCs: 0/29)
  - On the **internal side of neoprene isolator gloves and sleeves**
  - In **86.2%** (25/29) of the samples collected on the outside of infusion bags prepared within isolators (**3.3%** within BSCs: 1/30)

\* **B. FAVIER** et al. Evaluation de la contamination de l'environnement matériel et humain par le 5-fluoro-uracile lors de la manipulation en unités de reconstitution des chimiothérapies. *J Pharm Clin* 2001 ; 20 : 157-162



## IV. Rhône-Alpes 2006-2007 study

- **Objectives:**

- **Evaluate environmental contamination with 5FU** at various hospital sites, including **drug preparation and administration areas**
- **Observe practices** during the **preparation of cytotoxic drugs**
- **Compare the results with those obtained in the preliminary study**

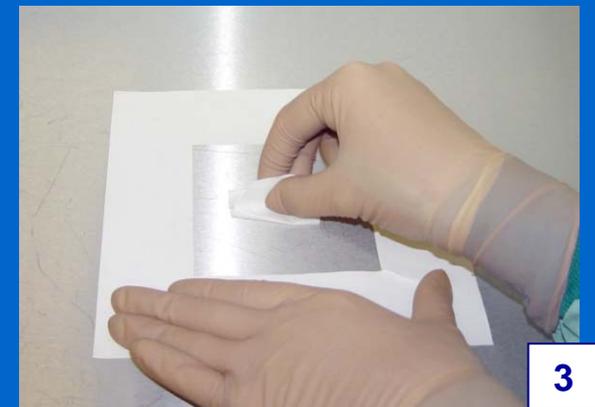
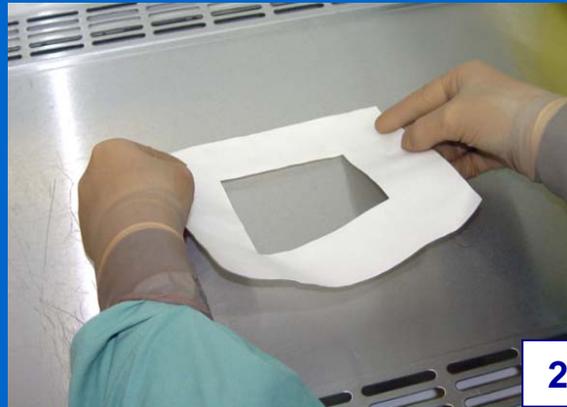
- **Methods:**

- **Selection of the sampling locations:** potential areas of contamination on the basis of the results of previous studies
- **During/after drug preparation:** at least 2 samples on the work surface within BSCs or isolators, 2 samples on gloves and 2 samples on the outside of infusion bags

## II. Rhône-Alpes 2006-2007 study

### ■ Sampling procedure:

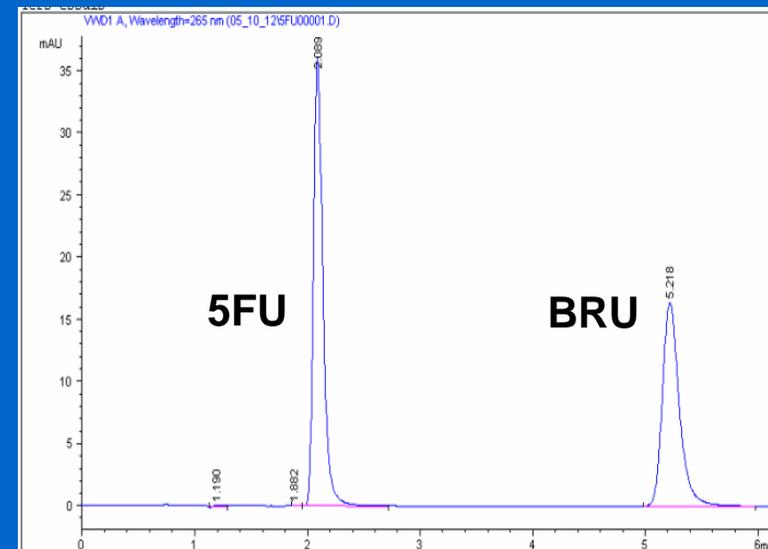
- Wipe sampling of objects and surfaces with moistened filters
- Calibration of surfaces when possible
- Gloves and outside of infusion bags: sampling by immersion



## II. Rhône-Alpes 2006-2007 study

### ■ Analytical procedure:

- Analyses performed by reverse-phase High-Performance Liquid Chromatography (HPLC) with ultraviolet-light detection (265 nm)
- Internal standard : 5-bromouracil (BRU)
- Mobile phase: water, acetic acid and heptanesulfonic acid sodium salt
- Flow: 0.5 ml/min
- Limit of quantification: 1.5 ng/cm<sup>2</sup>
- Limit of detection: 0.5 ng/cm<sup>2</sup>



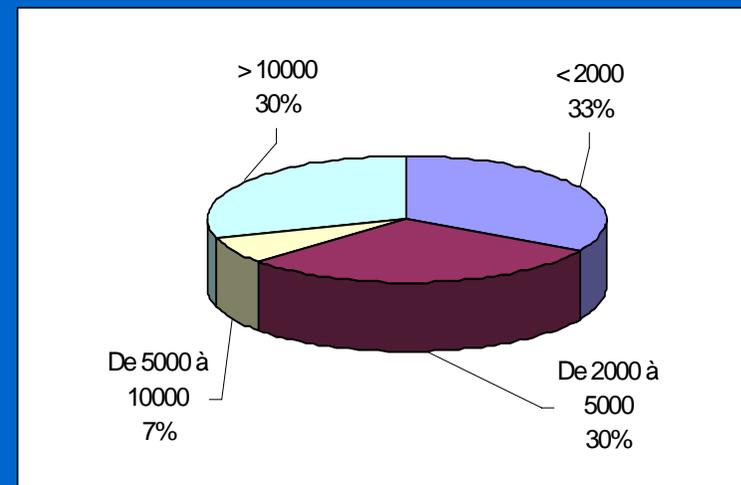
## II. Rhône-Alpes 2006-2007 study

### ■ Involvement of 30 voluntary hospitals:

- 2 teaching hospitals (5 hospitals)
- 14 public general hospitals
- 4 semi-private hospitals (1 cancer treatment centre)
- 6 private hospitals
- 1 military hospital

### ■ Description of the preparation of cytotoxic drugs:

- 325 to 33 100 preparations in 2005
- Amounts of 5FU up to 13.5 kg in 2005
- **Preparation under the pharmacist's responsibility:** 24 hospitals (16 using BSCs and 8 using isolators)
- **Preparation under nurses' responsibility:** 6 hospitals (all using BSCs)

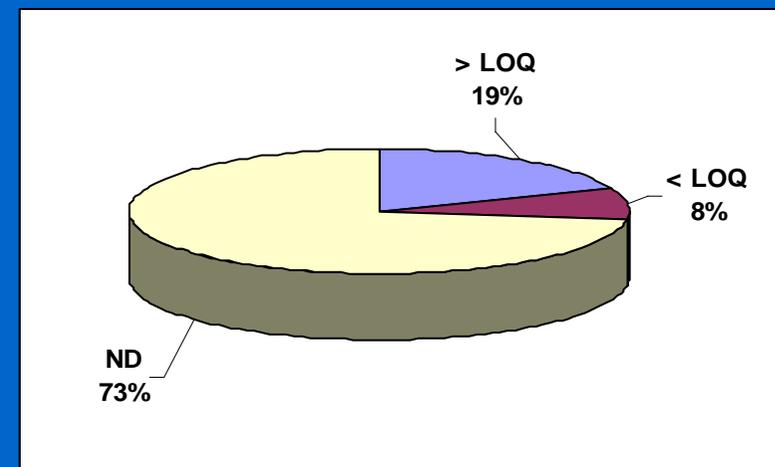




## II. Rhône-Alpes 2006-2007 study

- **555 samples** collected:
  - **473** in the **drug preparation areas**
  - **82** in the **areas where the drugs are administered**
  - No results for 3 samples (interference with the analysis method)
- Measurable amounts of 5FU: **27.5% of samples** (152 positive samples)
  - **28.3%** in the **drug preparation areas** (133 positive samples)
  - **23.2%** in the **areas where the drugs are administered** (19 positive samples)

*LOQ = limit of quantification*  
*ND = not detected*





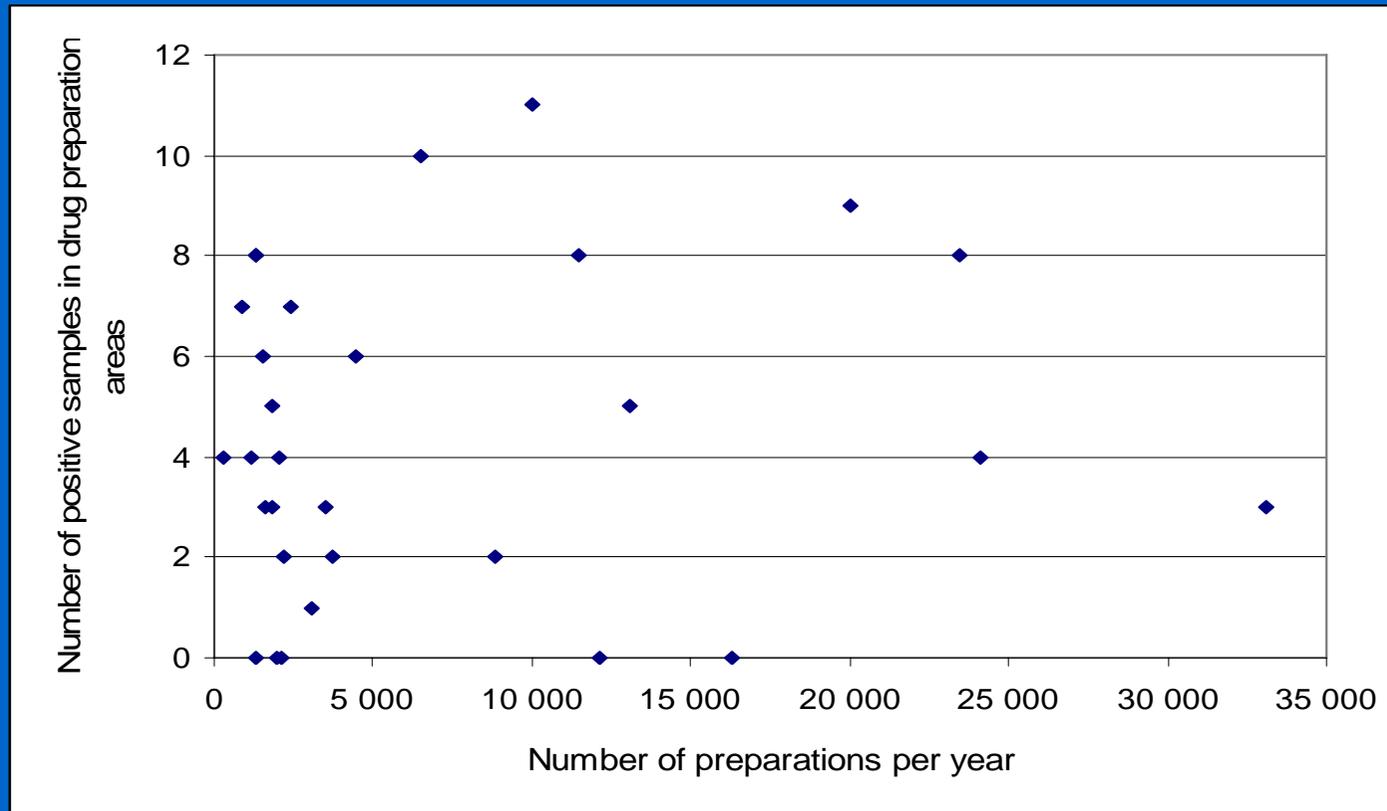
## II. Rhône-Alpes 2006-2007 study

- **Drug preparation areas:** proportion of samples found contaminated with 5FU
  - Work surfaces within BSCs and isolators: **32.7%** (53/162)  
→ **Up to 2 µg/cm<sup>2</sup>**
  - Surfaces outside BCSs and isolators in the immediate preparation areas: **14.2%** (16/113)  
→ **Up to 22 ng/cm<sup>2</sup>**
  - Outer gloves used for the preparation: **63.9%** (39/61)  
→ **Up to 1 mg/pair of gloves**
  - Outside of infusion bags: **20.0%** (12/60)  
→ **Up to 30 µg/infusion bag**
  - **No trace of 5FU detected on the internal side of neoprene isolator gloves and sleeves**



## II. Rhône-Alpes 2006-2007 study

- Drug preparation areas :



No relationship between the number of samples found contaminated and the amount of cytotoxic drugs prepared



## II. Rhône-Alpes 2006-2007 study

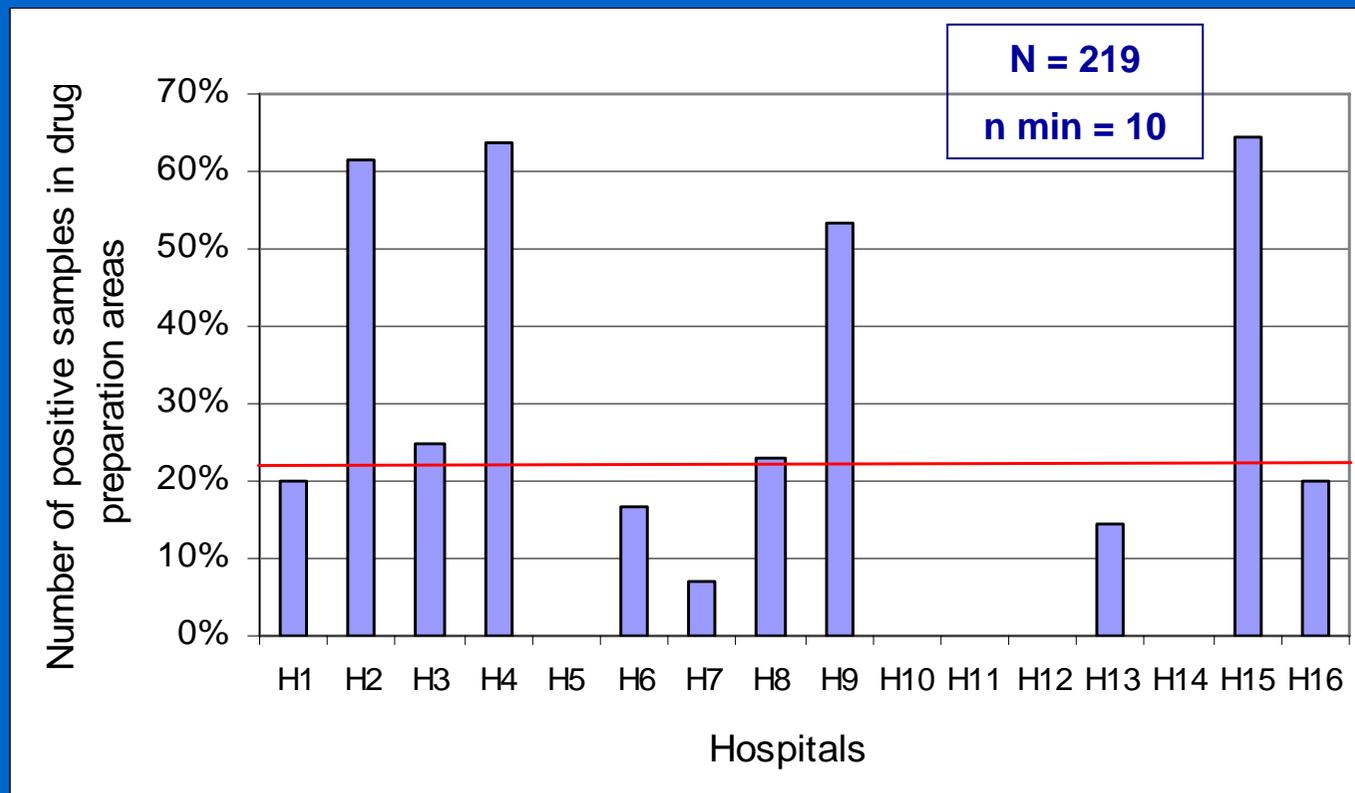
### ■ Drug preparation areas :

- Hospitals using BSCs, where the preparation is under the pharmacist's responsibility: **21,9 %**
  - Hospitals using isolators, where the preparation is under the pharmacist's responsibility: **34,4 %**
  - Hospitals using BSCs, where the preparation is under nurses' responsibility: **48,1 %**
- These findings emphasise the **need to centralise cytotoxic drug preparation under the control of a pharmacist**: financial penalties in 2008 for hospitals not correctly organized
- Wide variation in the hospitals' results within the 3 categories



## II. Rhône-Alpes 2006-2007 study

- BSCs, preparation under the control of a pharmacist:

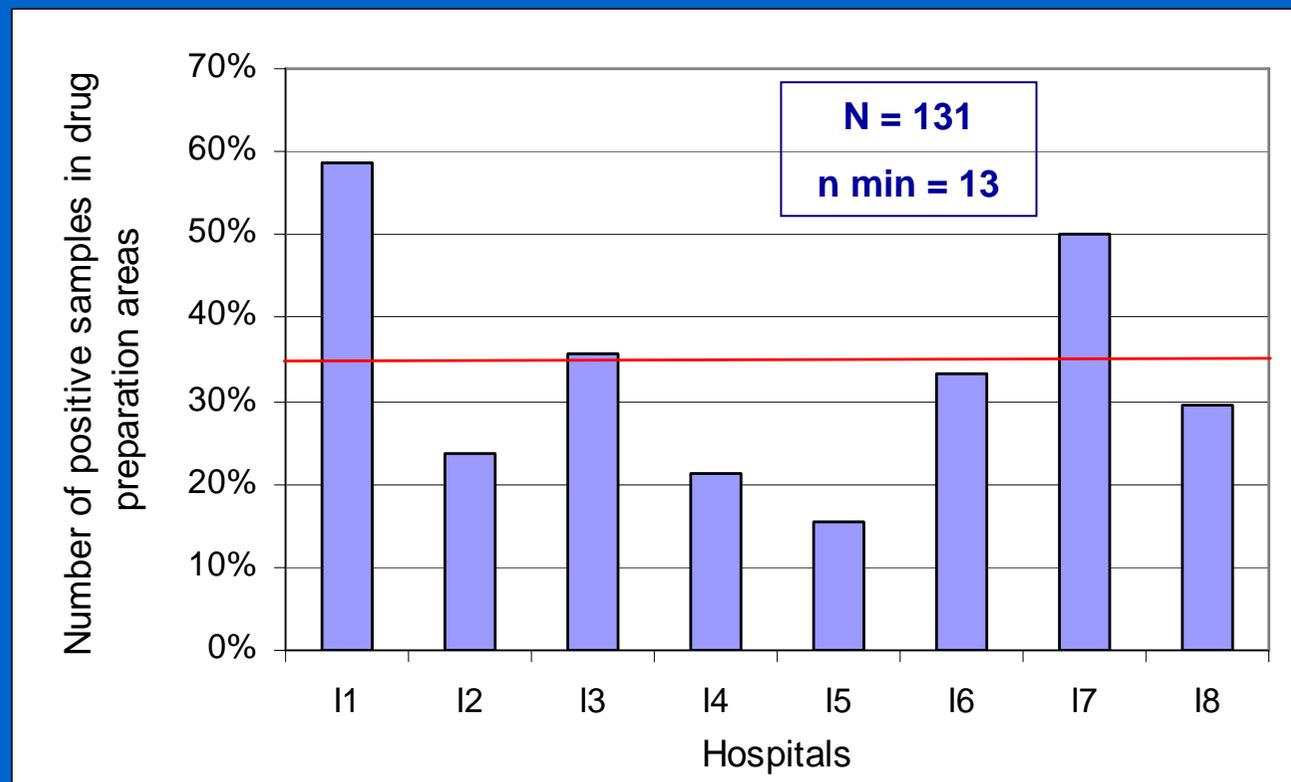


Level of contamination per hospital in the immediate preparation areas



## II. Rhône-Alpes 2006-2007 study

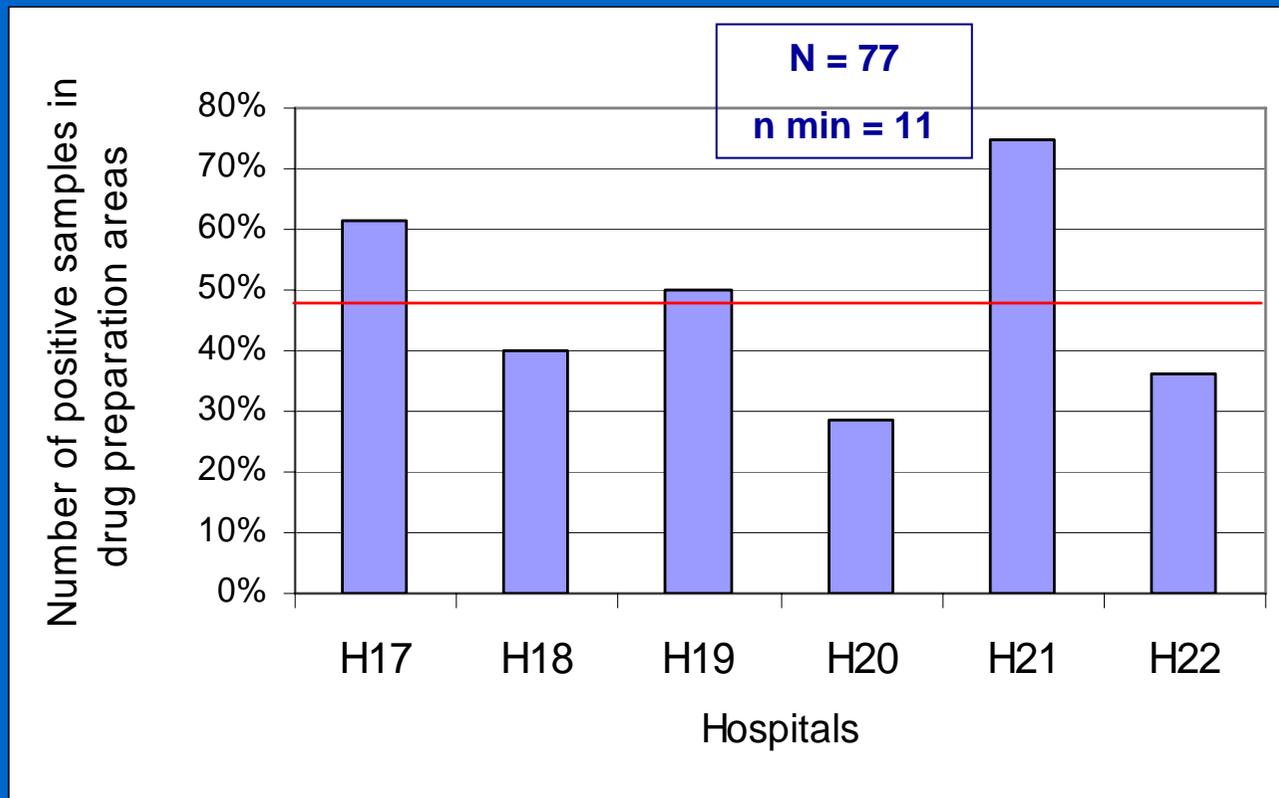
- Isolators, preparation under the control of a pharmacist:



Level of contamination per hospital in the immediate preparation areas

## II. Rhône-Alpes 2006-2007 study

- BSCs, preparation under the control of nurses:



Level of contamination per hospital in the immediate preparation areas

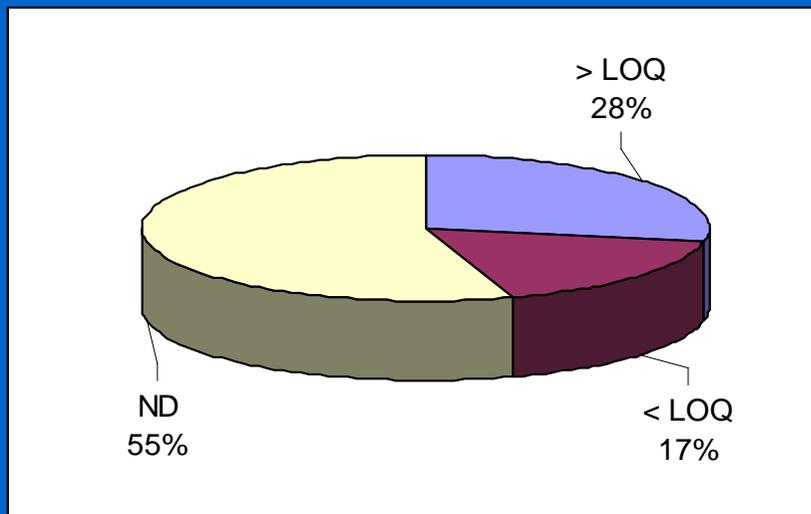


## II. Rhône-Alpes 2006-2007 study

- **Wide variation in practices for the preparation of cytotoxic drugs:**
  - **Use of venting devices with hydrophobic filters:**
    - \* BSCs, preparation under the pharmacist's responsibility: **81.5%** of hospitals (13/16)
    - \* Isolators, preparation under the pharmacist's responsibility: **62.5%** of hospitals (5/8)
    - \* BSCs, preparation under nurses' responsibility: **50.0%** of hospitals (3/6)
  - **Double gloving for hospitals using BSCs:**
    - \* Preparation under the pharmacist's responsibility: **100.0%** of hospitals
    - \* Preparation under nurses' responsibility: **16.7%** of hospitals (1/6)
  - **Changing of the outer pair of gloves:**
    - \* BSCs, preparation under the pharmacist's responsibility: **from every 15 min to no removal**
    - \* Isolators, preparation under the pharmacist's responsibility: **from every 20 min to every 3 h**
    - \* BSCs, preparation under nurses' responsibility: **every 15 min**

## II. Rhône-Alpes 2006-2007 study

- Areas where the drugs are administered:
  - Contamination of nurses' gloves **after the connection of infusion bags** to the administration devices: **33.3%** (5/15 samples)
  - Contamination of nurses' gloves **after the disconnection of infusion bags**: **100.0%** (only 3 samples collected)



Level of contamination of nurses' gloves after the connection/disconnection of infusion bags

*LOQ = limit of quantification*  
*ND = not detected*



## II. Rhône-Alpes 2006-2007 study

- **Conclusions:**
  - **Largest study** carried out in this field in France
  - Need to **centralise cytotoxic drug preparation under the control of a pharmacist**
  - Need to **elaborate guidelines** on the basis of those results and to **promote their use in our region**
  - Need to perform **another similar study in 2009** in order to estimate the **impacts of this kind of controls in terms of improvement of quality of practices**
  - Need to perform a **largest study in drug administration areas**, including **nurses' gloves**



### III. French regulatory background

- **Official governmental guidelines: December 2007 (ready since 2002...)**
  - « Good Practices for Pharmaceutical Preparations »
    - Chapter 7: « Products at risk for operators or the environment »
    - **Recommendation** of environmental controls « useful for quality insurance »
    - Difference with an **obligation** as *legionella* controls in water .....
  
- **Financial penalties** (no reimbursement of expensive drugs) for hospitals without centralised preparation unit under pharmaceutical control



## IV. Limits and future prospects

- Analytical limits: **5FU**, **anthracyclines**, cyclophosphamide, Pt ?
- Which markers in the future?

Drugs	Nb of preparations (2007)
FLUOROURACIL	5 540
DOXORUBICIN	3 133
CISPLATIN	2 630
CYCLOPHOSPHAMIDE	2 510
ETOPOSIDE	2 131
DOCETAXEL	1 777
PACLITAXEL	1 735
IRINOTECAN	1 532
CARBOPLATIN	1 391
OXALIPLATIN	1 282
IFOSFAMIDE	1 279
GEMCITABINE	1 243
HERCEPTIN	1 175
VINCRISTIN	1 152
BEVACIZUMAB	1 002
..... 92 different drugs	



## IV. Limits and future prospects

- **Frequency of the controls?**
  
- **Can we find an agreement on what could be an « acceptable low level »?**
  
- **ONCORA Laboratory:**  
Try to have a maximum of customers (700 French hospitals with a chemotherapy activity) to develop our analytical capacities / abilities
  
- **ONCORA network and local pharmacies:**
  - Maintain a high standard of quality / safety in daily preparations / administrations
  - Control it with an adapted frequency