

# Monitoring TDS indicators in France: updated results

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# Background

## Public health concerns

- Decrease in **sperm quality** in several countries
- Proved increase of **testis cancer** incidence in several developed countries
- Possible increase of **urogenital birth defects**
- Sperm quality **linked to life expectancy** (Jensen TK, 2009, Eisenberg 2014)
- Impairment of human gamete quality could impact **next generations' health**

**Testicular  
dysgenesis  
syndrome  
TDS**  
(Skakkebaek,  
2001)

## Environmental concerns

- Wide growing use of EDCs since the 50's in most countries: pesticides, drugs, food contaminants etc.

## Concerns about human exposures

- EDCs measured in all human matrices (blood, urine, milk etc.)

## Weight of evidence on causal links

- WHO/UNEP report, 2012
- Prioritized indicators (Le Moal *et al.*, 2015)

# Monitoring TDS indicators in France

## Overall objectives of the project

- To help estimating the health impacts and costs of EDC exposures and identifying corrective measures;
- To help anticipating and managing the ensued public health problems;
- **To assess the impact of public health interventions in the future.**

## Aim of the work

- To describe and quantify **nationwide** TDS indicators and their evolution;
- To provide data in support of, or against, existing causal hypotheses, e.g. role of EDC exposure;
- If necessary to generate new hypotheses.

# Semen quality: methods

## The FIVNAT Database

- Recorded most of assisted reproductive technology (ART) attempts in metropolitan France between 1989-2005
- On each record, two spermograms available per man, performed in separate laboratories

## The study population

- Men close to general population: partners of naturally infertile females (both tubes either blocked or absent), no selection about the man's fertility
- 26,609 males, aged 18-70 years

## Indicators

- Concentration in million sperm/ml
- Morphology in % morphologically normal form
- Total motility in % motile sperm

## Descriptive study

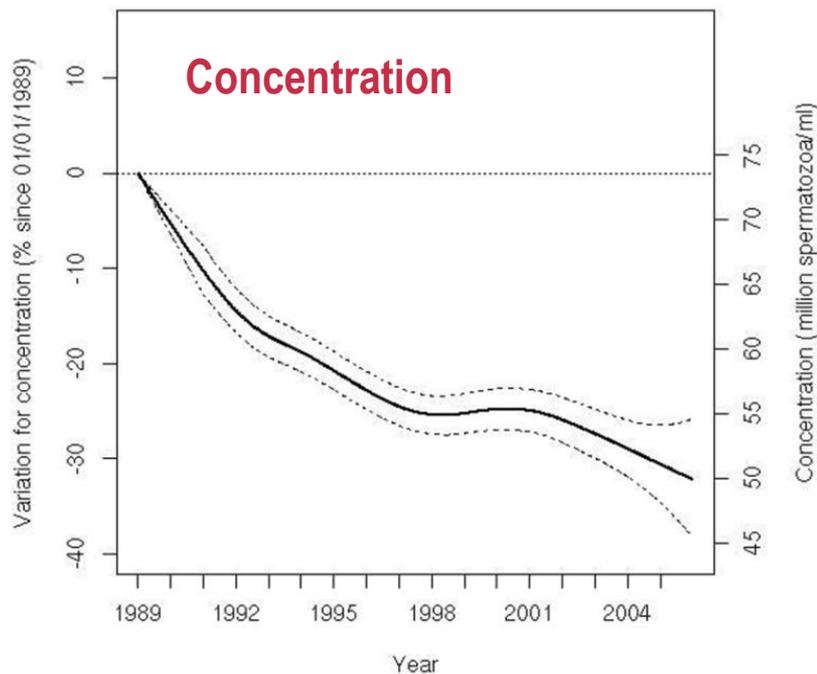
### Analyses of national time trends

- Generalized additive model

### Declination on regional scale

- Spatio-temporal model

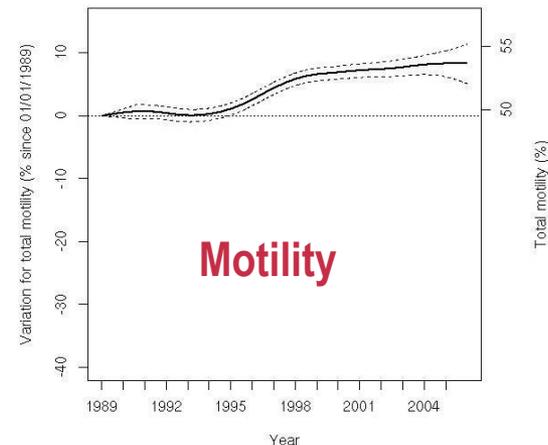
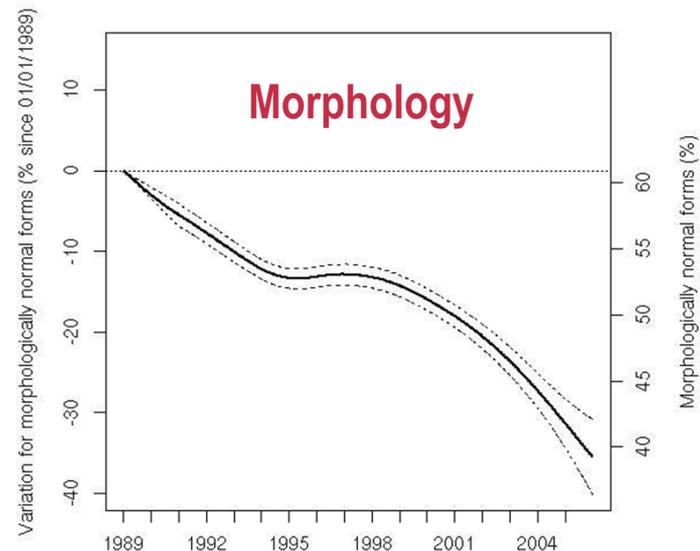
# Semen quality: national time trends



**Decrease in concentration: 1.9%/year between 1989 and 2005**

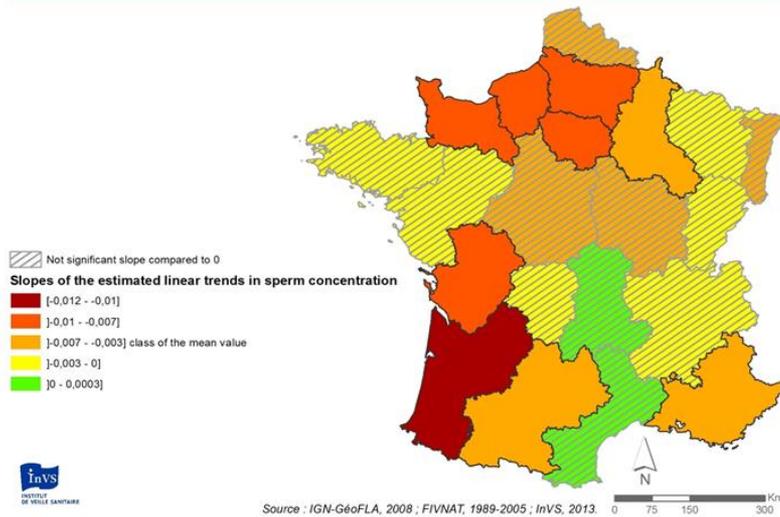
**- 32.2%** [26.3-36.3] = from 73.6 M spz/ml [69.0-78.4] to 49.9 M spz/ml [43.5-54.7]

(Rolland M, Le Moal J *et al.*, *Human Reproduction* 2013)

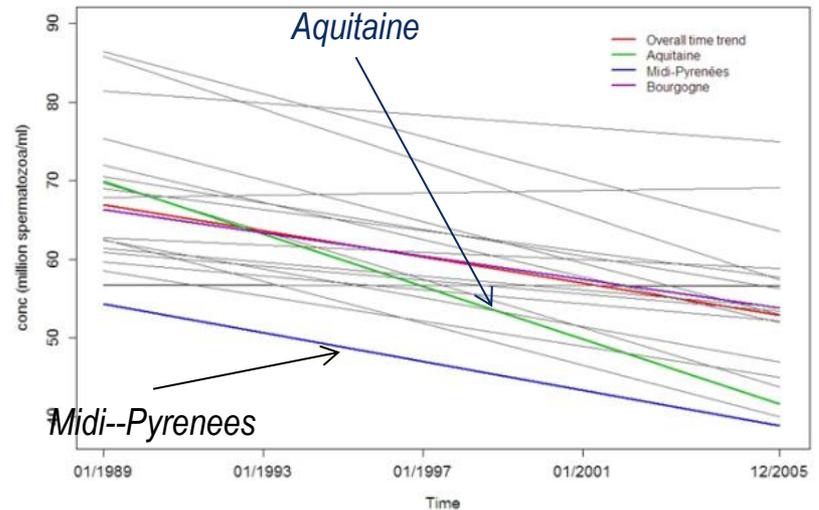


# Semen quality: regional time trends

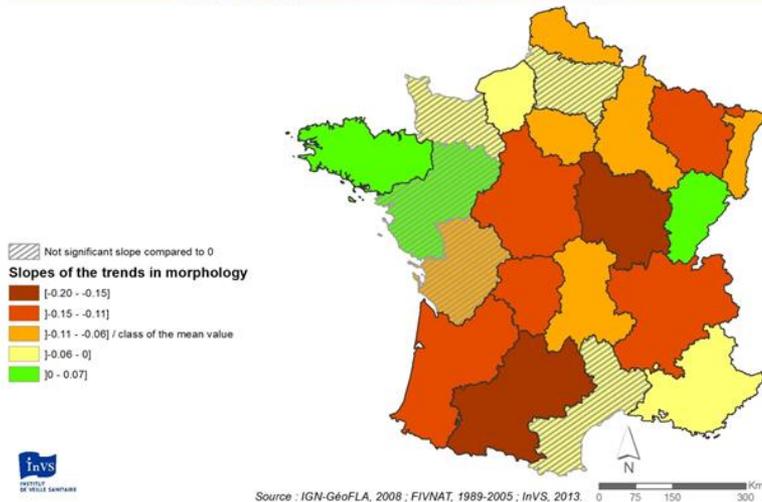
Regional time trends in sperm concentration in France from 1989 to 2005



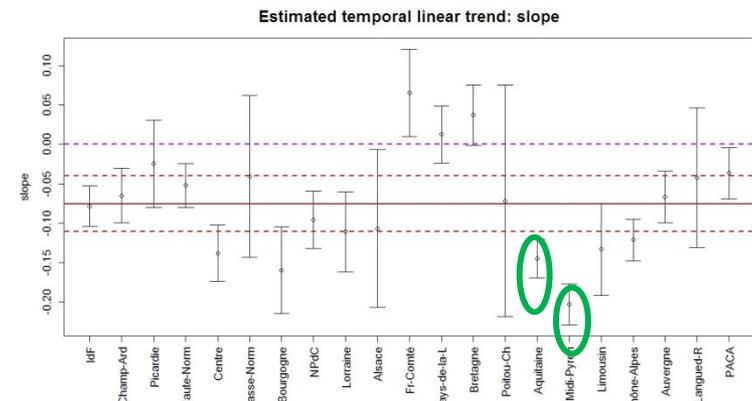
Estimated trends for concentration 1989-2005



Regional time trends in sperm morphology in France from 1989 to 2005



Estimated trends for morphology 1989-2005

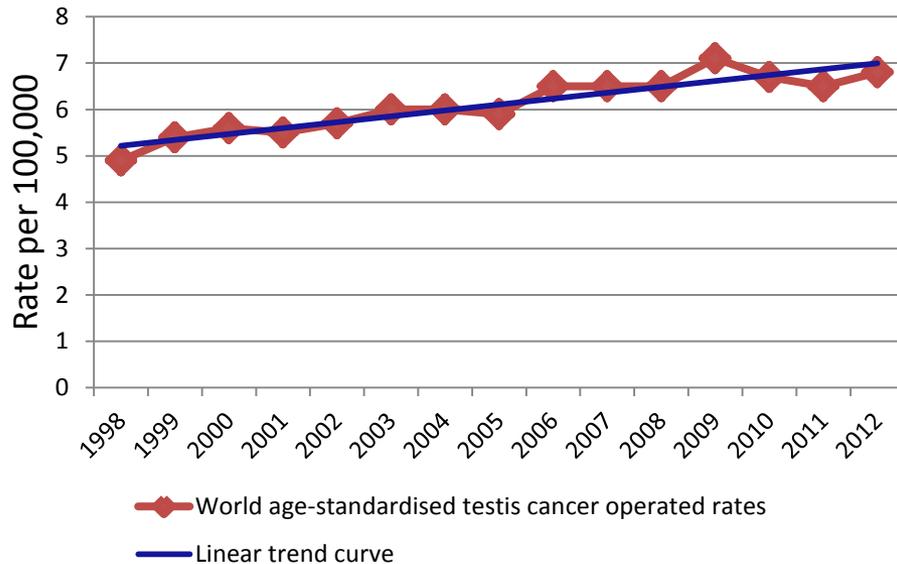


# Semen quality: conclusions

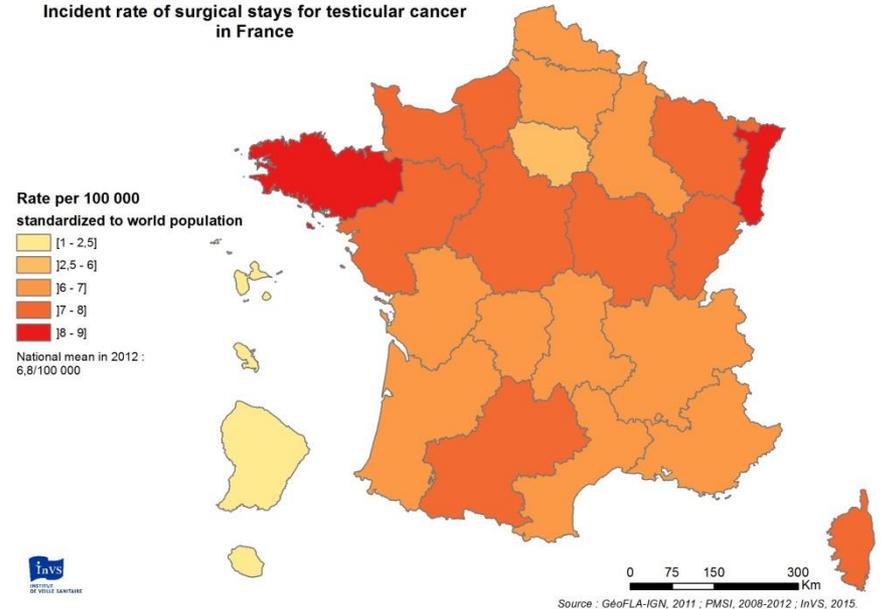
- The largest sample of men close to the general population studied in the world, 17 years follow-up, nationwide
- Robust results
- Decline (concentration and morphology) observed in almost all French regions
- Consistent with a global change in environmental exposure (does not seem to fit with lifestyle shifts, according to available data)
- **Serious public health warning**

# Testicular cancer (updated)

World age-standardised testis cancer operated rates, France 1998-2012



Incident rate of surgical stays for testicular cancer in France



Incidence rate of surgical stays for testicular cancer, **1998-2012**, whole France

Rate in 2012: 6.8/100 000 (N= 2202)

**Increase : 2.5 %/ year** (Kudjawu Y *et al.*, 2011)

**Unchanged trends** (previously 1998-2008)

**Robust results**

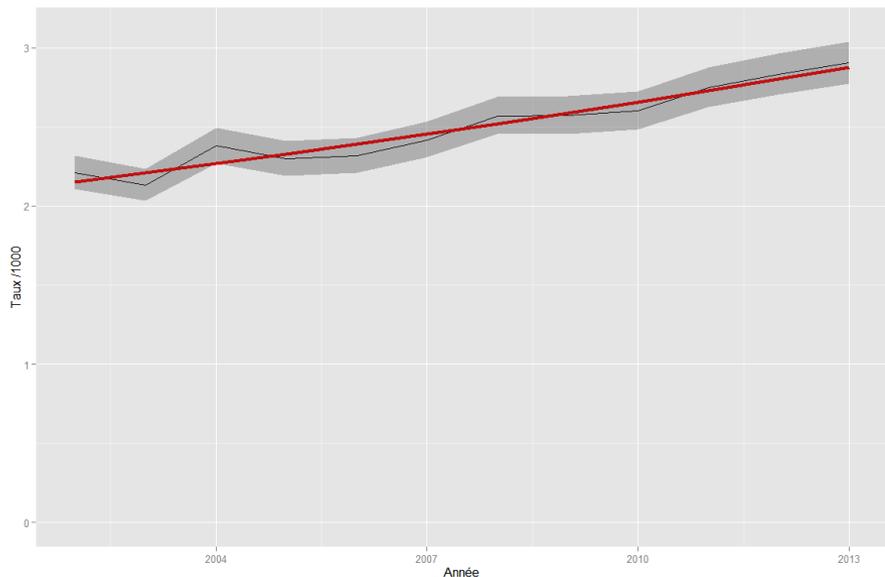
## Spatial trends 2008-2012

High incidences in far West and East  
 Lower in the South (except in Midi Pyrenees and Corse)

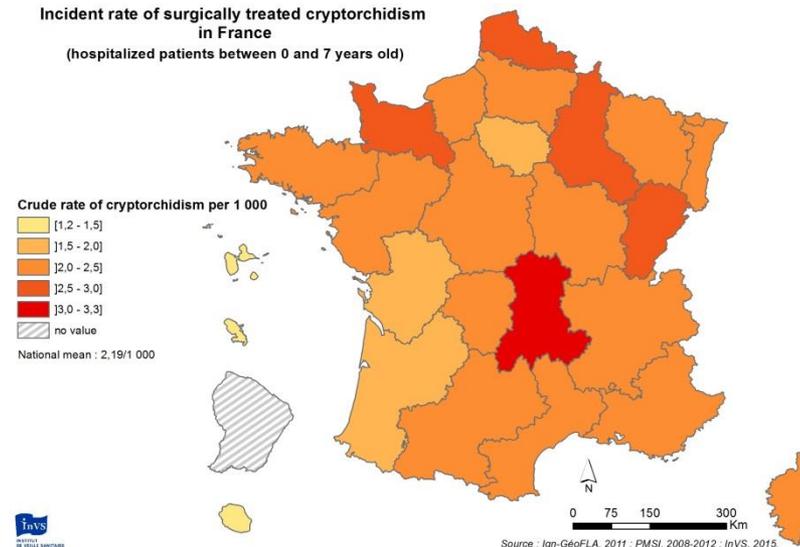
The lowest incidences are in ultramarine regions.

# Cryptorchidism (updated)

## *undescended testis*



Incident rate of surgically treated cryptorchidism in France (hospitalized patients between 0 and 7 years old)



Incident rate of surgically treated boys under 7 years for cryptorchidism, **2002-2013**, whole France

Mean rate in the study period: 2.5 /1000 (N = 6932)

**Increase: 2.68 %/ year**, 95% credibility interval [2.28-3.09]

**Previous results confirmed and amplified**

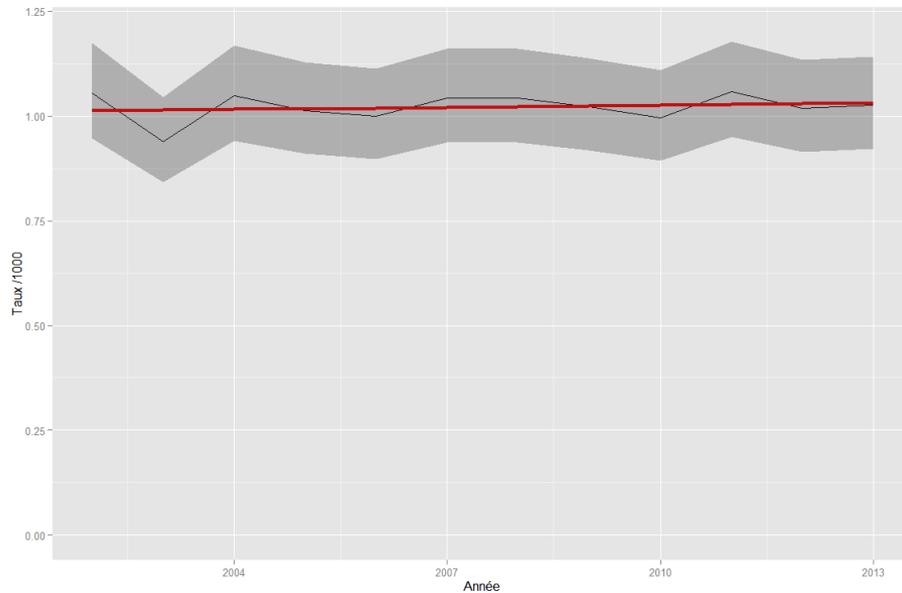
Increased robustness (exhaustivity of data, identification of incident cases)

**Spatial trends 2008-2012**

High incidence in Auvergne, the lowest in ultramarine regions

# Hypospadias (updated)

*malposition of the urinary opening*



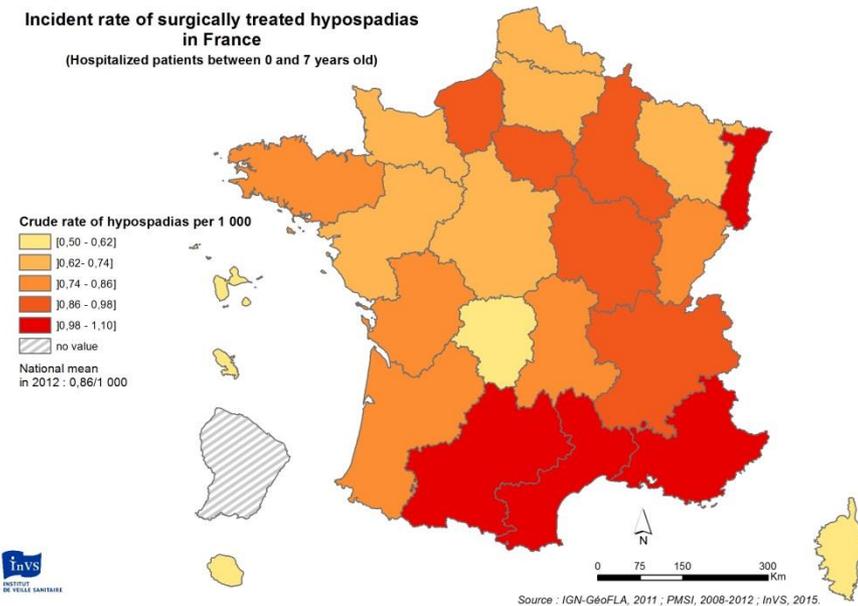
Incident rate of surgically treated boys under 7 years for hypospadias, **2002-2013**, whole France

Mean rate in the study period: 1.03/1000 (N=2870)

## Steadiness

The faint increase that was previously observed is no more discerned.

Incident rate of surgically treated hypospadias in France  
(Hospitalized patients between 0 and 7 years old)



## Spatial trends 2008-2012

High incidences in Alsace and South, low in Limousin, Corse and ultramarine regions

# TDS indicators in France: overall results

- The 4 TDS indicators can be **nationwide monitored** using existing data bases (cost-efficient)
- **Consistent temporal trends**, long periods, in a country of 65 M inhabitants
- Impairment of male reproductive health since the 90's, possibly since the 70's for sperm quality
- A warning about male reproductive health in France and a **public health warning**
- **Spatial heterogeneity**, but no consistency among indicators, except for ultramarine regions
- No Western/Eastern trends observed in France
- **Limits:** patients are located at the time of diagnosis (hospital data) or indirectly (sperm data)
  - Rough proxy for environmental exposures
  - Relevant time of exposure is not the same for the 4 TDS indicators

# Interpretation of results

## **Environmental changes affecting the whole population**

- Possibly consistent with EDC increasing exposure since the 50's
- Other or mixed causes: lifestyle
  - Increase in tobacco smoking in mothers
  - Nutritional or metabolic factors affecting parents (possible role of EDCs)
  - Stress, health, sleep disturbance (sperm quality)
- Unidentified factors

# Steps forward

## Next steps

- Spatio-temporal analyses for all TDS indicators
- Other reproductive health indicators: **precocious puberty** (poster A. Rigou *et al.*)

## In the longer term

- **Prioritized indicators** (in the context of EDC exposure) : breast and prostate cancers, sex ratio, endometriosis, fibromas (poster J. Le Moal *et al.*)
- Indicators of residential exposure for several risk factors (e.g. pesticides, socio-economics)  exploratory analyses of their effects to explain spatial trends
- Localization **at birth**

# Key issues remaining

- Growing evidences on the relations with EDC exposure (WHO-UNEP report, 2012), but a striking lack of human data
- **Is a global impairment of human reproductive health currently happening?** [not only fertility outcomes]
- **How would human reproductive health evolve in the future?**
- Creation of a scientific network named **HURGENT** for **Human Reproduction and General Environment Network**
- Aiming at designing a reproductive health monitoring system to be shared between participating countries (poster J. Le Moal *et al.*)
- 10 involved countries : France, Denmark, Finland, UK, Poland, Hungary, Israel, Czech Republic, Netherland, US

 **Need for monitoring reproductive health at an international level**