**Risk factors of childhood leukemia:
the French research program**

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Childhood leukemia: main hypotheses

▸ **Environment**
   Ionising radiation
   Extremely low-frequency - electromagnetic fields (ELF-EMF)
   Air pollution
   Pesticides
   Passive smoking

▸ **Infections and immune system**
   Specific infections
   Hygiene hypothesis

▸ **Genetic factors**
   Family history of leukemia
   Genetic factors (GWAS)
   Genetic susceptibility to environment

Slide 1:

Epidemiology of childhood leukemia

Variations in incidence Space-time clustering

Ecological studies

Cohort studies

Case-control studies
- **Interviews**
- **DNA**

GEOCAP (GIS)

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RNHE

National Registry of Childhood Hematopoietic malignancies 1990, INSERM, Villejuif

Inserm research unit of Environmental Epidemiology of Cancer

National Registry of Childhood Solid Tumors 2000, CHU de Nancy

Accuracy and precision of diagnoses
Exhaustiveness

Slide 2:

Epidemiology of childhood leukemia

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Domestic radon exposure and childhood leukemia

Lucie et al,1990	UK	ALL	+
Henshaw et al, 1990	13 countries	Leukemia	+
Butland et al, 1990	7 countries	Leukemia	+
Alexander et al, 1990	UK	ALL	+
Muirhead et al, 1991	UK	Leukemia	+
Collman et al, 1991	USA	Leukemia	+
Foreman et al, 1994	UK	Leukemia	-
Richardson et al, 1995	UK	Leukemia	+
Thorne et al, 1996	UK	AML	+
Kohli et al, 2000	Sweden	ALL	+
Evrard et al, 2005	France	ALL/AML	=/+

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IRSN

▶ **Ecological assocation AML x radon**

Leukemia   Radon
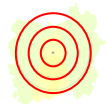
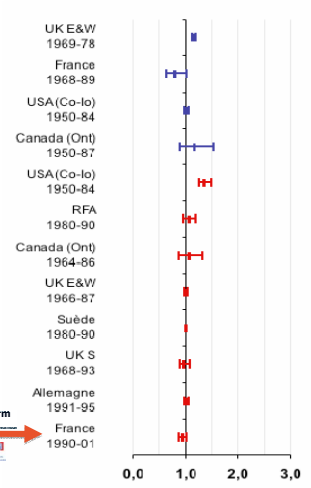*Evrard et al, Eur J Cancer Prev 2005*
Evrard et al, Health Physics, 2006

Vicinity of nuclear sites and childhood leukemia
multisite studies

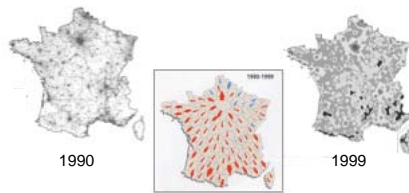→ Distance from sites (SIR ≈ 1)
White-Koning et al, Br J Cancer 2004

→ Modelled exposure of the *commune* (SIR ≈ 1)
Evrard et al, Br J Cancer 2006

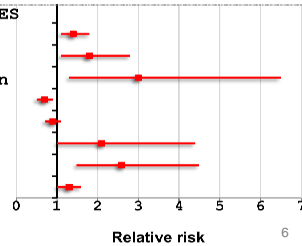**Specific infection and childhood leukemia**

Population mixing

⇒ Incidence increased with population mixing in rural isolated municipalities
- At the place of birth
  Rudant et al, Eur J Cancer 2006
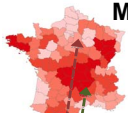- At the residence at diagnosis
  Bellec et al, Br J Cancer 2007
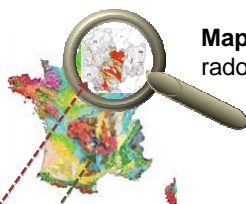
The GEOCAP study
Domestic radon exposure

Measurement campaigns IRSN

Mapping the geogenic radon potential IRSN

Geolocation (GIS)
- Registry cases (9,000 leukemia cases)
- population controls (30,000 children)

Case-control study

Epidemiology of childhood leukemia

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The GEOCAP study:
Nuclear sites

Modeling the discharges IRSN
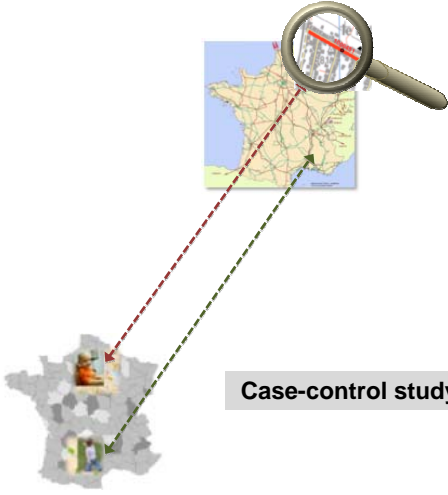
Geolocation (GIS)
- Registry cases (9,000 leukemia cases)
- population controls (30,000 children)

Case-control study

Epidemiology of childhood leukemia

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The GEOCAP study:
Living next to powerlines

Mapping the lines
Quantifying EMF-ELF
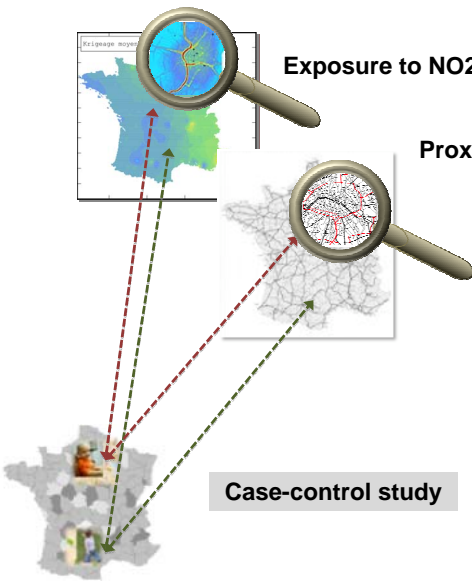
RTE

Geolocation (GIS)
- Registry cases
  (9,000 leukemia cases)
- population controls
  (30,000 children)

Case-control study

Epidemiology of childhood leukemia

Inserm

The GEOCAP study:
Traffic and air pollution

Exposure to NO2 and benzene

ADEME
Agence de l'Environnement
et de la Maîtrise de l'Energie

Proximity to main roads

NAVTEQ
MAPS & TRAFFIC.

GEOCIBLE
le géomarketing

Geolocation (GIS)
- Registry cases
  (9,000 leukemia cases)
- population controls
  (30,000 children)

Case-control study

Epidemiology of childhood leukemia

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Slide 11

The GEOCAP study: **In-depth case-control studies:**

Nuclear   Rn   ELF-EMF   NO$_2$,Bz   Traffic

Interviews
Residential history
Confounders

DNA
GWAS
Gene-environment interactions

Permanent survey
Objective assessment of exposure based on GIS

2010 ESTELLE **study**
2003 ESCALE **study**
1995 ADELE **and** ELECTRE **studies**

Slide 12

In-depth case-control studies
Environment

Association with maternal use of insecticides

Menegaux et al, Occup Env Med, 2006
Rudant et al, Env Health Persp, 2007

Maternal use of insecticides during pregnancy

Association with neighbouring gas stations (benzene?)

Steffen et al, Occup Env Med, 2004
Brosselin et al, Occup Env Med, 2008

Adele – hosp 1995-99
300 AL / 300 Co

Escale – national 2003-04
1500 K / 1700 Co

F   2006 Menegaux
BR   2006 Pombo de Oliveira
F   2008 Rudant

0   1   2   3   4   5   6
Relative risk
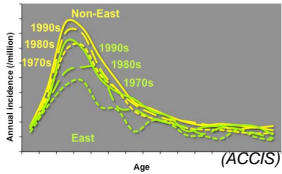
In-depth case-control studies
Infections, hygiene hypothesis

Incidence peak of ALL higher and earlier with growing socio-demographic conditions

⇒ Hygiene improvement?
- Delayed common infections
- Decrease in breastfeeding   *Greaves, 1988*

Deregulated response

ALL

Preleukemic clone
t(12;21) TEL-AML1
MLL, hyperdiploidy

Early common infections

(Guthrie spots)

Regulated response

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In-depth case-control studies
Inverse associations with markers of early common infections

Repeted early infections

Perrillat et al, Br J Cancer 2002 •
Jourdan da Silva et al, Br J Cancer 2004 •
Rudant et al, 2009 (in revision) •

Day-care attendance

Perrillat et al, Br J Cancer 2002 •
Jourdan da Silva et al, Br J Cancer 2004 •
Rudant et al, 2009 (in revision) •

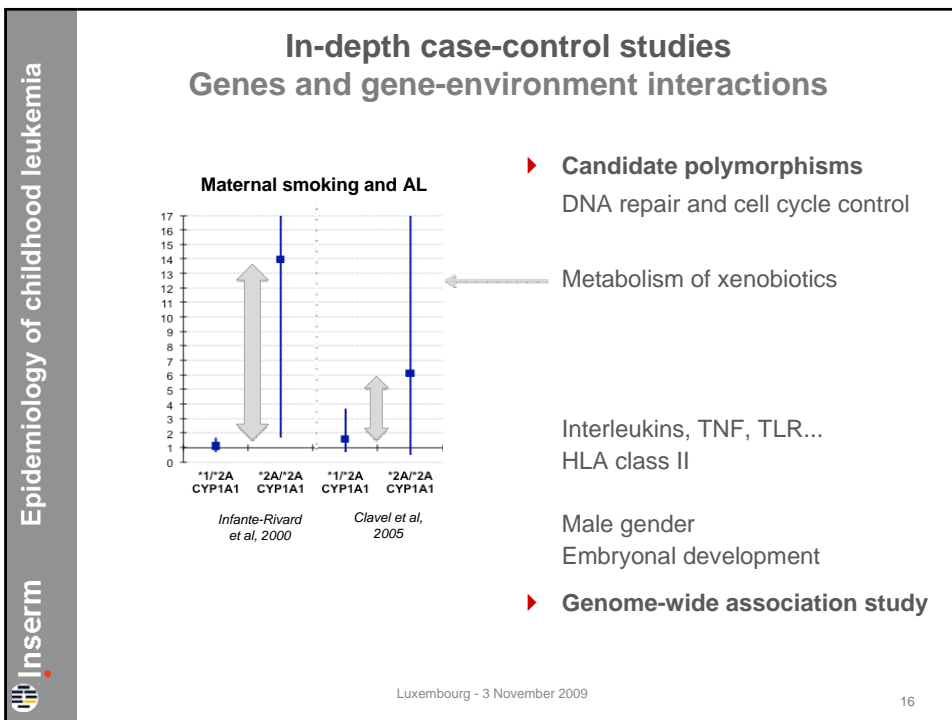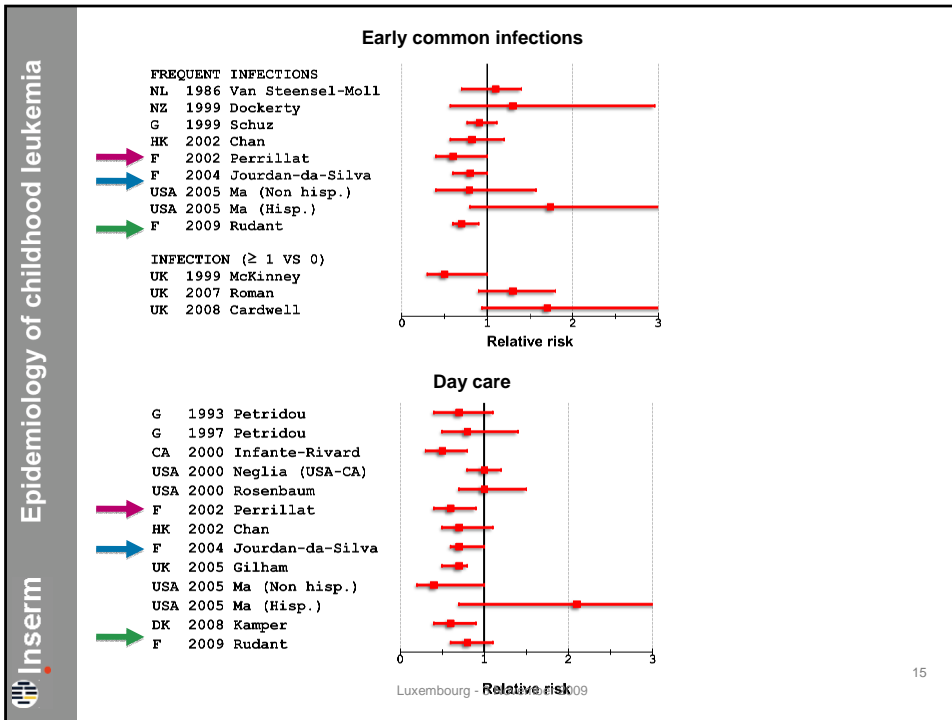**Adele – hosp 1995-99**
300 AL / 300 Co

Breast-feeding

Perrillat et al, Eur J Pediatr 2002 •
Rudant et al, 2009 (in revisionl) •

Electre – pop 1995-99
500 AL /600 Co

Escale – national 2003-04
1500 K / 1700 Co   14

Early common infections

FREQUENT INFECTIONS
NL   1986 Van Steensel-Moll
NZ   1999 Dockerty
G   1999 Schuz
HK   2002 Chan
F   2002 Perrillat
F   2004 Jourdan-da-Silva
USA 2005 Ma (Non hisp.)
USA 2005 Ma (Hisp.)
F   2009 Rudant

INFECTION (≥ 1 VS 0)
UK   1999 McKinney
UK   2007 Roman
UK   2008 Cardwell

Relative risk

Day care

G   1993 Petridou
G   1997 Petridou
CA   2000 Infante-Rivard
USA 2000 Neglia (USA-CA)
USA 2000 Rosenbaum
F   2002 Perrillat
HK   2002 Chan
F   2004 Jourdan-da-Silva
UK   2005 Gilham
USA 2005 Ma (Non hisp.)
USA 2005 Ma (Hisp.)
DK   2008 Kamper
F   2009 Rudant

Relative risk

In-depth case-control studies
Genes and gene-environment interactions

Maternal smoking and AL

*1/*2A CYP1A1   *2A/*2A CYP1A1   *1/*2A CYP1A1   *2A/*2A CYP1A1

Infante-Rivard et al, 2000

Clavel et al, 2005

▶ **Candidate polymorphisms**
  DNA repair and cell cycle control

  Metabolism of xenobiotics

  Interleukins, TNF, TLR...
  HLA class II

  Male gender
  Embryonal development

▶ **Genome-wide association study**

Funding

Public grants

Inserm (National Institute of Health and Medical Research)

INCa (National Cancer Institute)

ANR (National Research Agency)

Ministry of the Environment

InVS (National Agency of Public Health)

AFSSET (National Agency of health and security of the Environment)

AFSSAPS (National Agency of health and security of health products)

Charity associations

Fondation de France

Fondation pour la Recherche Médicale

Association pour la Recherche sur le Cancer,

Ligue contre le Cancer

Cent pour Sang la Vie,

Enfance et Santé

Fondation Wyeth

Institut Electricité Santé