Cancer risk associated to radon after exposure in mines or in homes

Research programs under EU coordination
Implications for risk management

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The “Uminers + Animal data” European project

Uminers + Animal data
Contract no. FIGH-CT1999-00013
Duration: Feb 2000 – July 2003
Coordinator : M Tirmarche (IRSN)

FP5

Quantification of lung cancer risk after low radon exposure and low exposure rate : synthesis from epidemiological and experimental data

- Epidemiology (cohorts of U miners in Europe)
- Modelling (confrontation of classical and TSCE modelling)
- Animal experiments

8 partners

IRSN (France), BfS (Germany), NRPI (Czech Republic), GSF (Germany), CEA (France), AEAT (UK), NRPB (UK), RIVM (The Netherlands)

Final report : **www.irsn.org**

The Alpha-risk European project

Specific targeted research or innovation project (STREP)
Contract no. 516483 (FI6R)
Duration: July 2005 – June 2008
Coordinator: M Tirmarche (IRSN)

FP6

Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures

- Epidemiological studies (U miners, nuclear workers) and radon in homes
- Organ dose calculation
- Risk assessment

18 partners

IRSN (France), BfS (Germany), NRPI (Czech Rep), CR-UK (UK), IARC (France), WSC (UK), AWE (UK), HPA (UK), U Salzburg (Austria), GSF (Germany), RIVM (The Netherlands), ISS (Italia), BAuA (Germany), CAATS (France), UK-AEA (UK), SCK-CEN (Belgium), U Ottawa (Canada) , RWE NUKEM (UK)

Web site : **www.alpharisk.org**

Reference documents

1988 IARC 43 « Man-made Mineral Fibres and Radon »

1993 ICRP 65 « Protection against radon-222 at home and at work »

1999 BEIR VI « Health effects of radon exposure »

2001 IARC 78 « Some internally deposited radionuclides »

2007 UNSCEAR R-654 « Sources-to-effects assessment for radon in workplaces and homes »

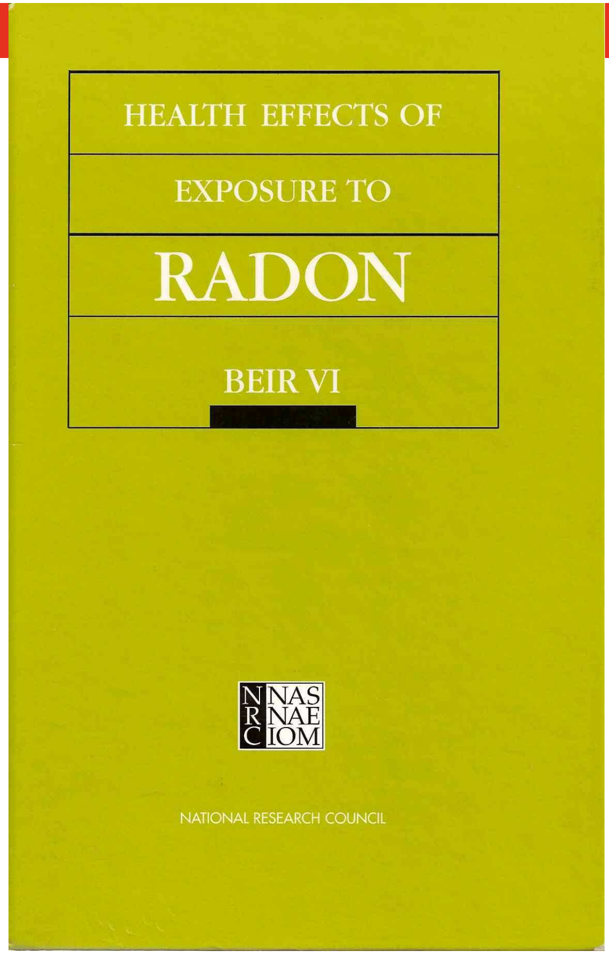
BEIR VI Report

11 cohorts

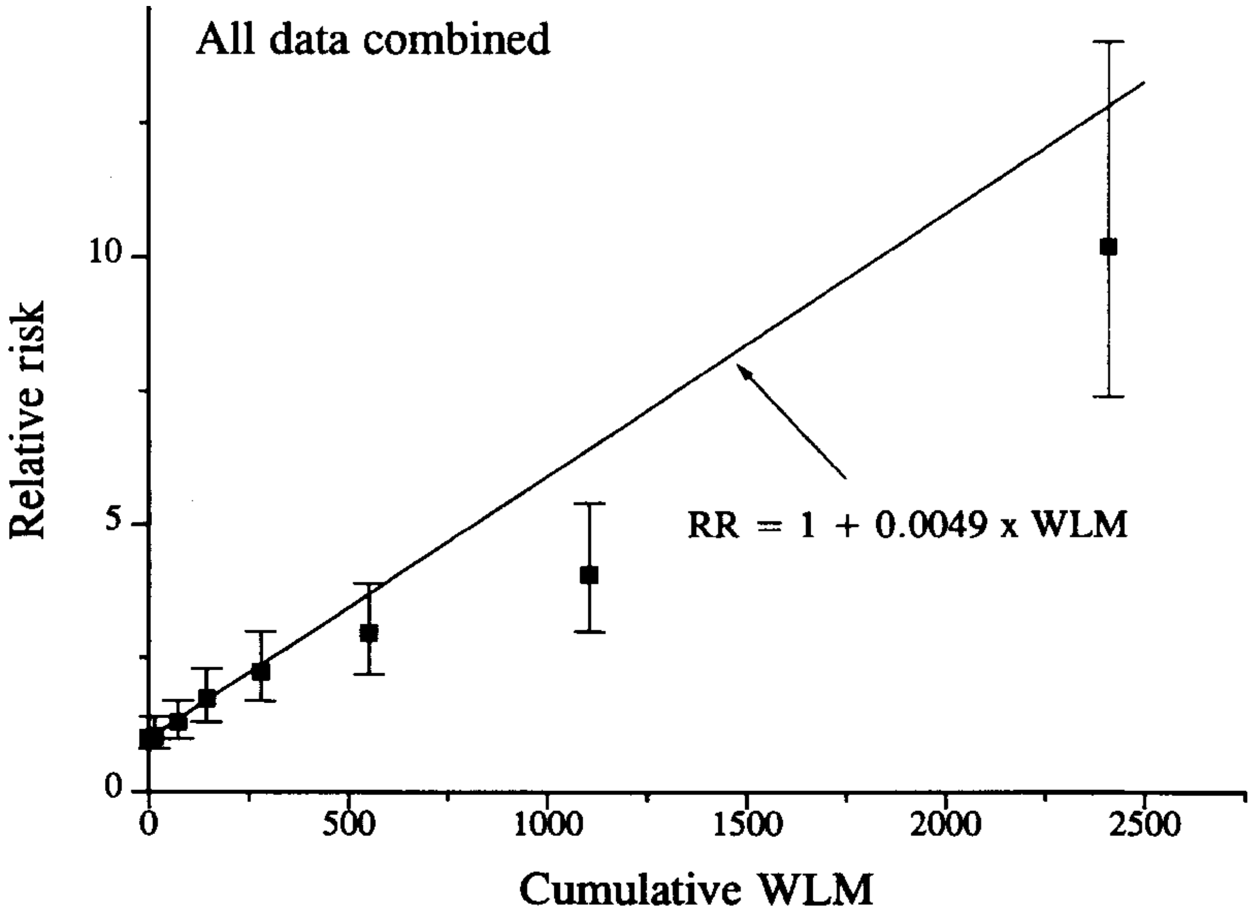
- > 60000 miners
- > 2600 lung cancer deaths

Results

- ERR/100 WLM   0.49 [0.2 – 1.0]
- Agreement with a linear model
- ERR ↘ with Time Since Exposure
- ERR ↘ with Age at Exposure
- inverse exposure rate effect
- sub-mutiplicative interaction with tobacco
- no increased risk except lung cancer



Lung cancer risk among miners



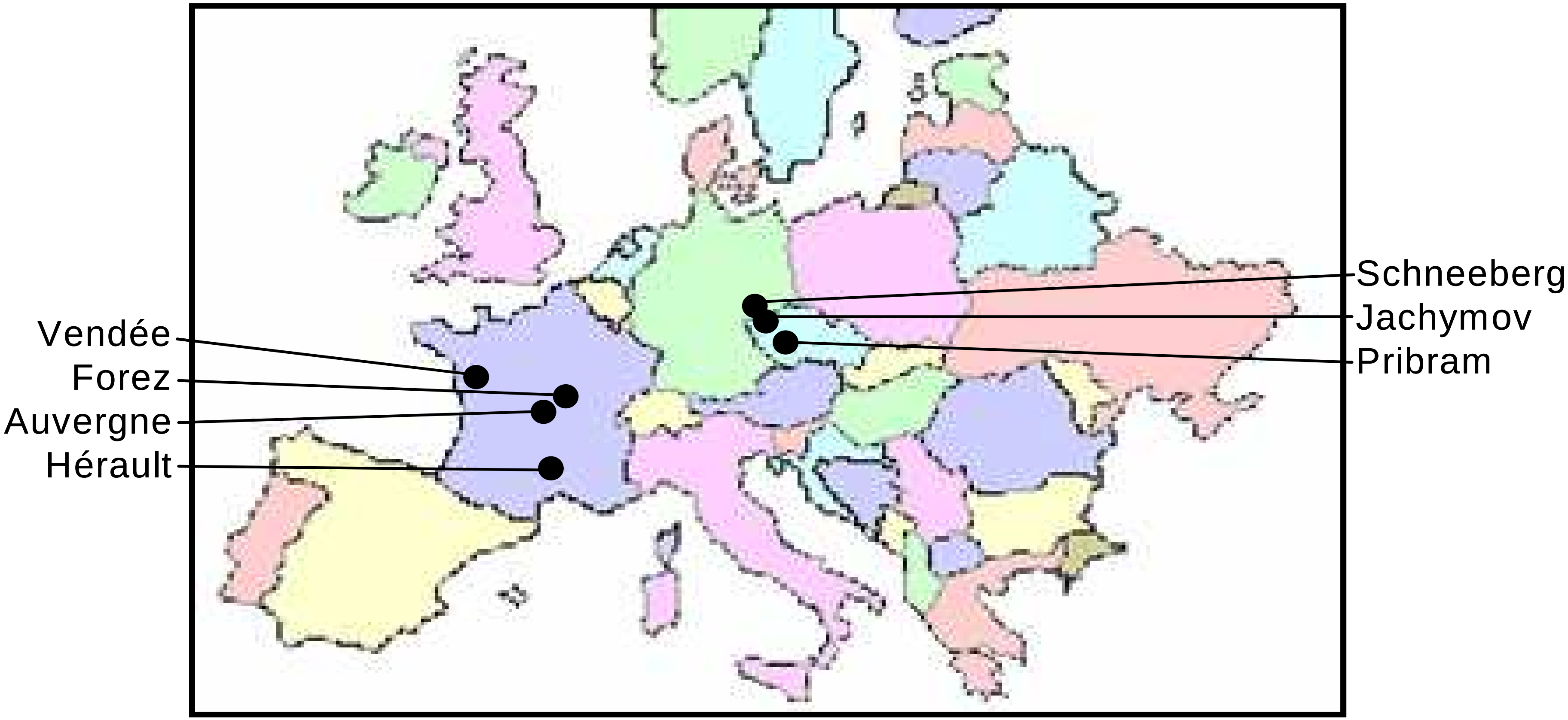
(from Lubin et al, NIH 1994)

BEIR VI preferred models

TSE age duration model		TSE age concentration model	
ERR/WLM	0.0055	ERR/WLM	0.0768
TSE (years)		TSE (ans)	
5 - 14	1.00	5 - 14	1.00
15 - 24	0.72	15 - 24	0.78
25 -	0.44	25 -	0.51
Attained age (years)		Attained age (years)	
-54	1.00	-54	1.00
55 - 64	0.52	55 - 64	0.57
65 - 74	0.28	65 - 74	0.29
75 -	0.13	75 -	0.09
Exposure duration (years)		Concentration (WL)	
-4	1.00	-0.5	1.00
5 - 14	2.78	0.5 - 1	0.49
15 - 19	4.42	1 - 3	0.37
20 - 24	4.42	3 - 5	0.32
25 - 34	6.62	5 - 15	0.17
35 -	10.2	15 -	0.11

(Beir VI, 1999)

Uranium mines in Europe



Points of research and objectives

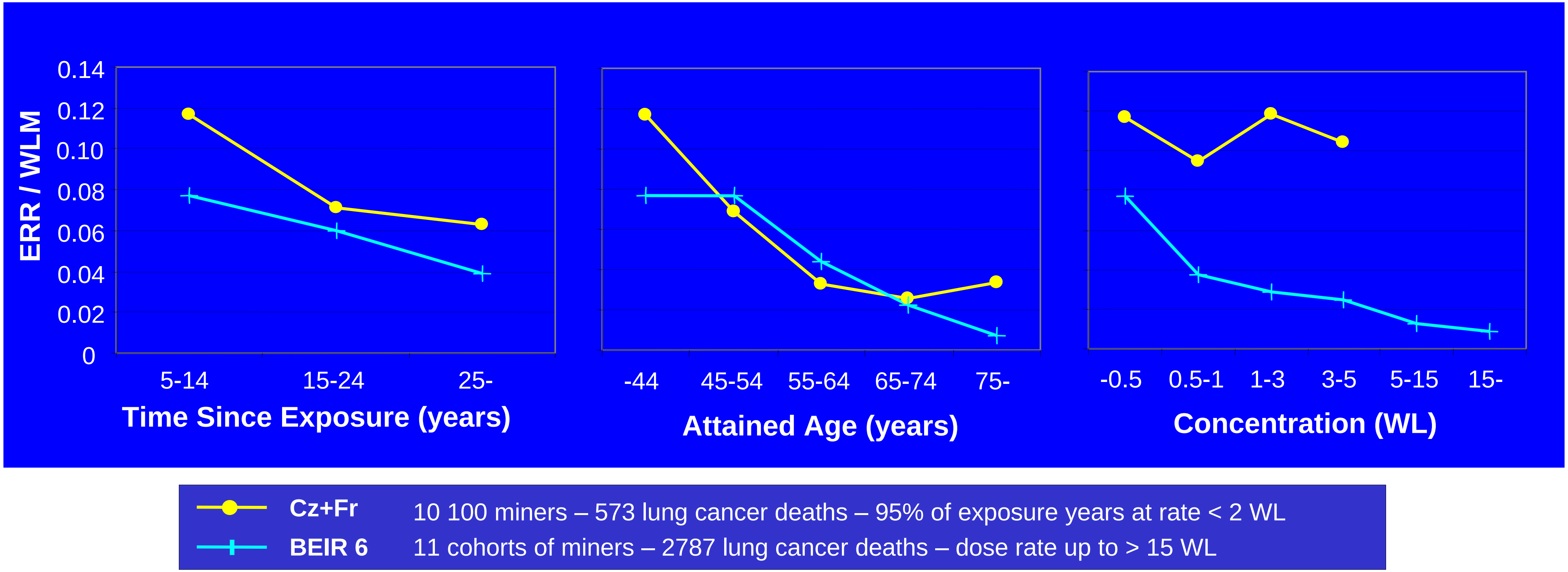
Extended follow-up and new cohorts :

- Increase statistical power for risk assessment of lung cancer deaths at low doses
- Allows modelling of the exposure-risk relationship (non parametric approaches, modifying factors, exposure rate effect…)
- Cohort studies give information on causes of death others than lung cancer
- Adjustment on other risk factors (arsenic, silica, diesel exhaust, smoking)
- External gamma radiation, LLRn dust inhalation : interaction on target organ ?
- Organ dose calculation and dose-risk modelling
- Incidence rather than mortality data : available ?

➡

- Exposure-dose correspondence ?
- Lifetime risk estimates ?
- ICRP recommendations ?

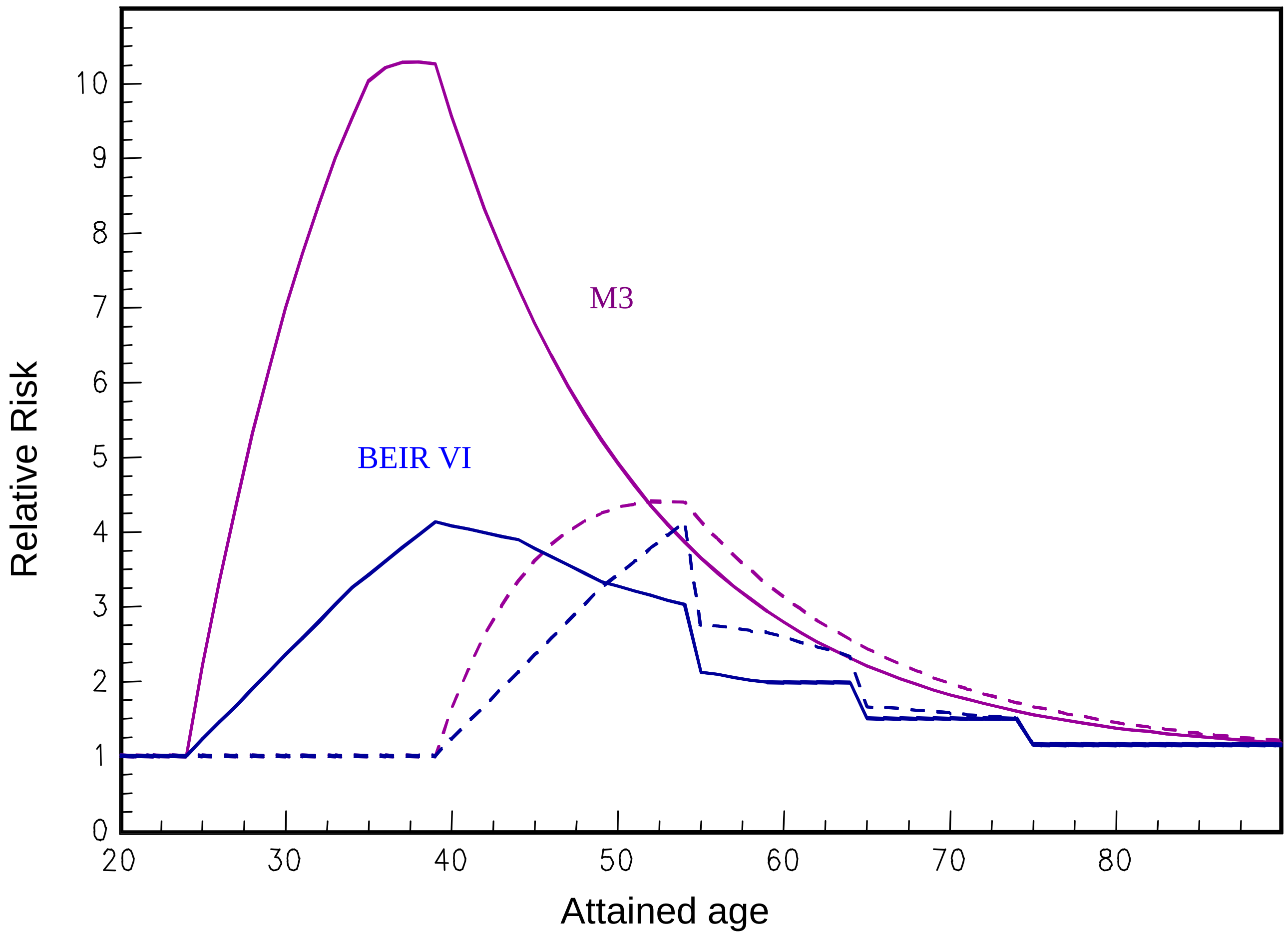
The Czech-French joint study: risk modifiers



Strong decrease of risk with time since exposure
No inverse dose-rate effect

The Czech-French joint study: effect of time and age

Relative lung cancer risk of lung cancer associated to a radon cumulated exposure of 90 WLM (6 WLM per year during 15 years)

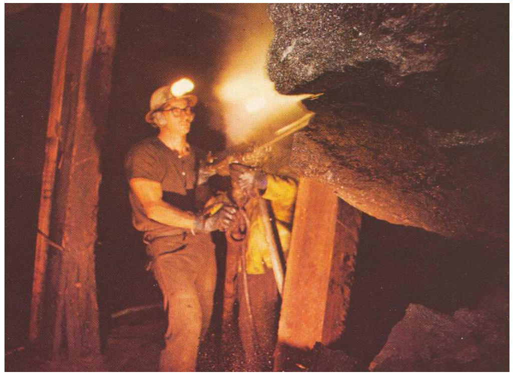


2 scenarii:
Exposure at age 20-34 years (solid lines)
Exposure at age 35-49 years (dashed lines)

2 models:
BEIR VI-age-concentration model (broken lines)
Cz-Fr preferred model (M3) (smoothed lines)

[Tirmarche et al, 2003]

Uranium miners studies



- **Cohorts of uranium miners** (WP1)
  - France, Czech Republic and Germany
  - (> 40,000 miners)
  - Nested case-control studies (tobacco, lung cancer and leukemia risk)
  - Good quality reconstruction of multiple exposures (radon, gamma, ore dust)

- **Methodology**
  - Dosimetric models (WP5)
  - Parametric statistical methods and biologically-based modelling approaches
  - Consideration of measurement errors and uncertainty

- **Objectives**
  - Time-modifier of the radon-lung cancer risk relationship
  - Risk associated to tobacco, radon and other radiation sources in the mines
  - Risk of cancers other than lung (leukemia, kidney…)
  - Non cancer mortality risk
  - Lifetime lung cancer risk estimates (WP6)
  - Parallel analysis with indoor radon studies (WP6)

Radon and decay products in homes

1. Epidemiology: Analytical versus ecological studies

a. Risk of lung cancer :
  - Results from a large number of national case-control studies,
  - Major information from joint analyses :
    - European,
    - North American studies
    - Future world pooling analysis
  - Experience through extrapolation from miners studies

b. Leukemia risk ?
  - Studies in adults, in childhood leukemia

Radon and decay products in homes

1. Risk management

a. Radon is a typical domestic pollutant, to be managed in parallel to other domestic agents

➔General public : risk per Bq.m[3]

b. Risk from chronic alpha exposure should be expressed in working environment, compared with risk from external exposure :

➔ multiple exposure, occupational exposure

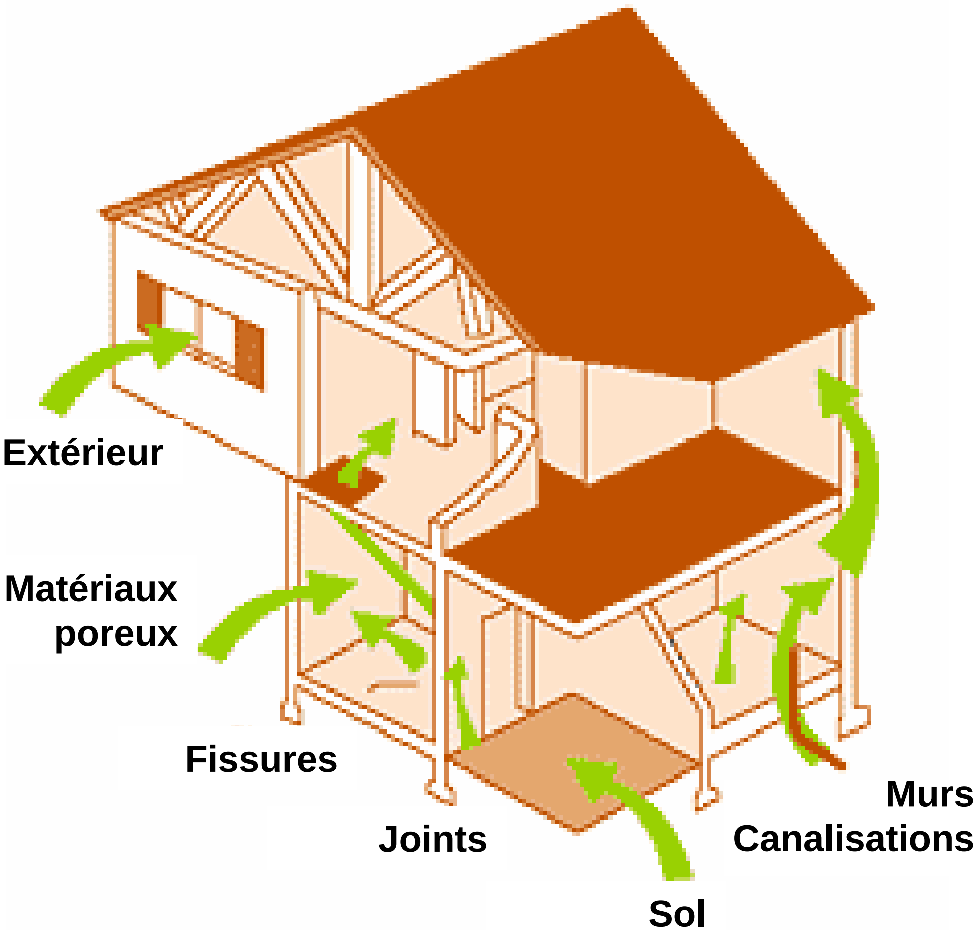
- Comparing risk at the same organ level :
  - input from dosimetry expertise
  - cumulated exposure : external and internal :dose expressed in Gy ?
  - discussion of quality factor, dose rate effect, experience from Uminers studies
  - differences of background rates as we are comparing different populations (ERR versus EAR, cofactors……)
  - Management through mSv limits ?

Radon risk at low annual exposure in houses ?

Gas : concentration is depending of underground characteristics, changes on geographical level,

seasonal corrections are needed

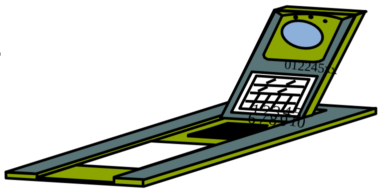
Habits of live should be taken in account, residence level…



1. Exposure is present everywhere, but at different concentrations
2. It is a chronic exposure, cumulated over life time

➔ Individual measurment

of exposure is necessary



➔best approach : case-control study

Case-control study of indoor radon and lung cancer in France

Results :

- Past exposure to radon reconstructed over a mean duration of 20 years
- Lung cancer risk increases with exposure to radon

RR = 1.04 per 100 $Bq.m^{-3}$ CI 95% = [0.99 – 1.11]

(adjusted on age, sex, region, smoking and occupational exposure)

RR = 1.07 per 100 Bq.m-3 CI 95% = [1.00 – 1.15]

(if limited to those with all houses measured)

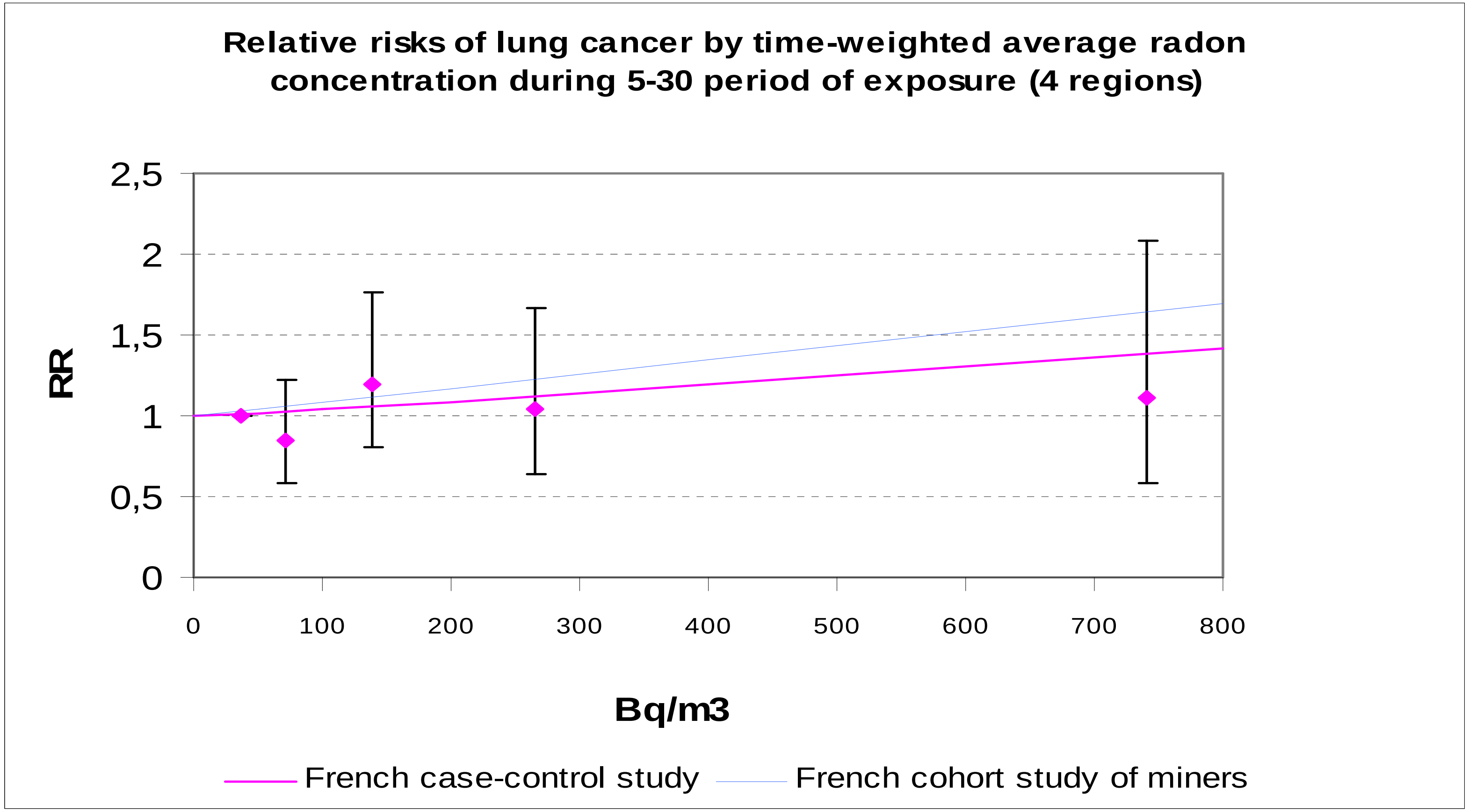
- This risk is low when compared to the risk associated to smoking
- This result is concordant with those from previous studies and with the risk extrapolated from miners studies

•publication in Epidemiology (Nov 2004,vol15, 6:709-716)

Integration in the European joint analysis (France, Belgium, Germany, UK, Sweden, Italy,,,)

➔ 7148 cases and 14208 controls included (in Darby et al : BMJ.2005;330:223-7)

Comparison of Risk from French U Miners and Case-control Study



RR=1.04 [0.99:1.11] per 100 Bq/m^3

25 WLM ⇔230 Bq/m^3 for 25 years

⇒ RR=1.008 per WLM

⇒ RR=1.09 per 100 Bq/m^3

From miners risk coefficient to indoor risk coefficient

If 1 WLM annual exposure in a mine is equivalent to an exposure to 230 Bq per m^3 over one year in a home

This assumes

Exposure duration : 2000 hours in mines versus 7000 hours in homes

Different breathing rates

Different equilibrium factors, particules sizes, attached fraction

Different co-factors :dust/smoking particles , others

Case-control studies in general population

- Comment : no other domestic pollutant has been studied in a more detailed way :
  - Evidence from animal experience, even at « low » doses
  - Evidence from occupational exposure
  - Evidence from 13 epi studies in Europe, 7 from North-America and two from China (plus 2 from Ural region)

Major input of case-control studies :

➔ in field epi studies, able to adjust precisely on individual tobacco consumption, including male and females, smokers and non-smokers

➔ meta-analysis

➔ joint analysis : increase of statistical power

➔*Darby et al. BMJ 2005 and Scand. J Work Environ Health 2006)*

➔*Krewski et al. Epidemiology 2005 and J Toxicology Environ Health, 2006)*

European case-control studies of residential radon and lung cancer

Study	Number of subjects with lung cancer	Number of control subjects
Austria	183	188
Czech Republic	171	713
Finland: nationwide	881	1435
Finland: south	160	328
France	571	1209
Germany: Eastern	945	1516
German: Western	1323	2146
Italy	384	405
Spain	156	235
Sweden: nationwide	960	2045
Sweden: never-smokers	258	487
Sweden: Stockholm	196	375
United Kingdom	960	3126
Total number of subjects	7148	14,208

North American and Chinese case-control studies of residential radon and lung cancer

Study	Number of subjects with lung cancer	Number of control subjects
New Jersey	480 f	442f
Winnipeg	488 m; 250 f	488 m; 250 f
Missouri 1	538 f	1183 f
Missouri 2	512 f	553 f
Iowa	413 f	614 f
Connecticut	527 m; 436 f	442 m; 507 f
Utah; southern Idaho	319 m; 192 f	587 m; 275 f
China		
Shenyang	308	356
Gansu	768	1659

Joint European study : Protocol and results

- Protocol
  - 13 studies / 9 countries :
  - Standardized protocol, same inclusion criteria, common questionnaire, reconstruction of exposure over last 35 years, inter-comparison of methods of measurments, 7 148 cas / 14 208 témoins

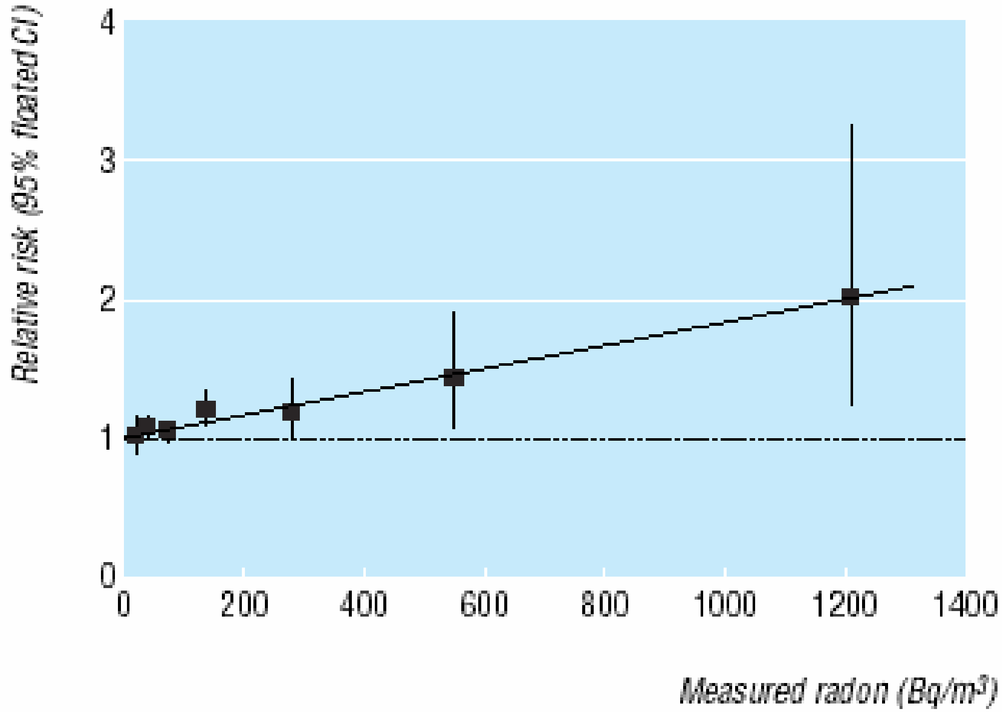
- Results : linear dose-response relationship

➡ Clear evidence of association: Lung cancer risk is increasing with cumulated radon exposure.

RR = 1,08 for 100 Bq/m³ [1,03 – 1,16]

➡ Significant relationship if limited to those exposed =< 200 Bq/m³

Significant increase for nonsmokers



[Darby et al, *BMJ* 2005]

EUROPEAN POOLING Study : non-smokers

Measured radon (Bq/m^3)	% who were lifelong non-smokers
<100	39
100-199	40
200-399	41
400-799	46
800+	48
p for trend	*0.001*

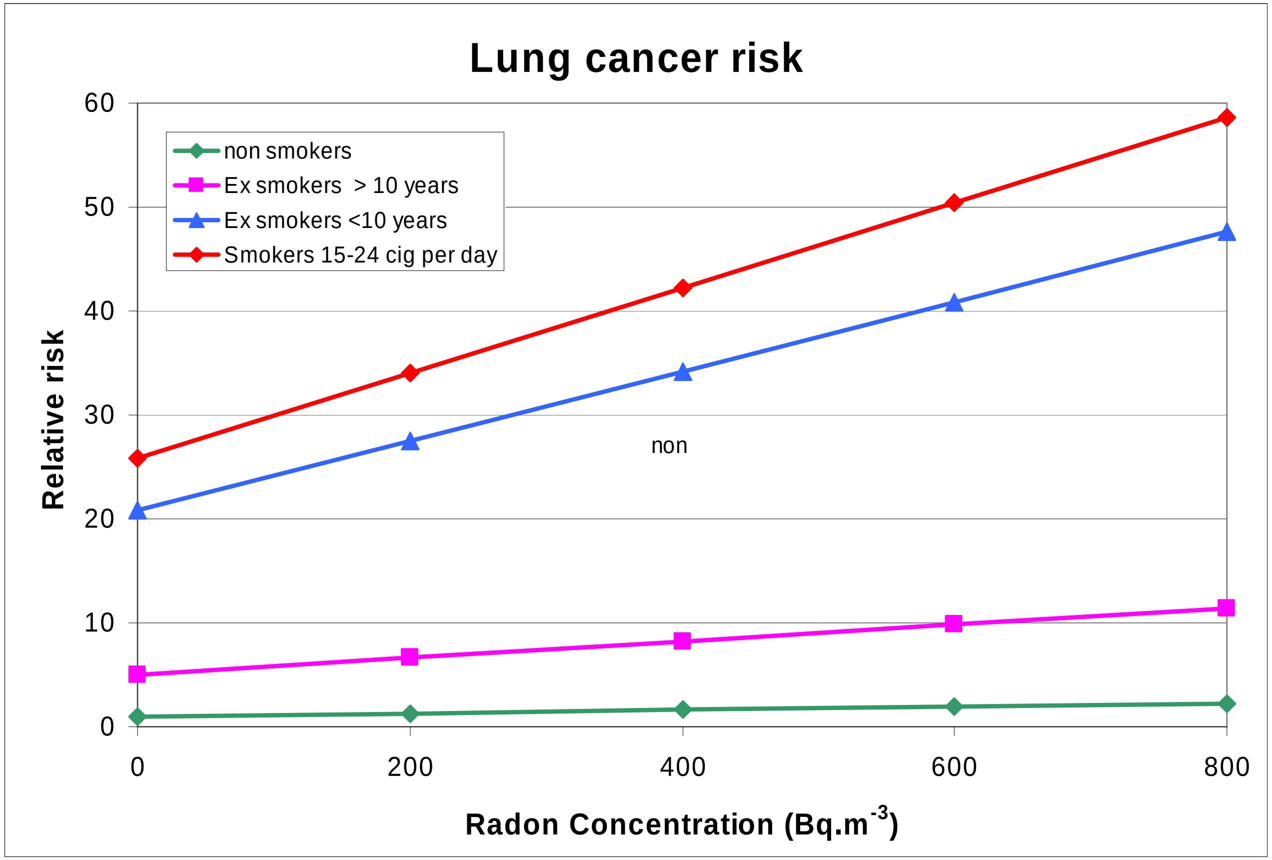
Percentages calculated after stratification for study, age, sex, and region of residence

EUROPEAN POOLING Study :

Effect of stratification for smoking

Stratification	% increase in lung cancer risk per 100 Bq/m³ measured radon	95% CI	p
A. Study, age, sex, region, smoking in 20 groups	8.4	(3.0, 15.8)	0.0007
B. Study, age, sex, region, smoking in 7 groups	5.2	(1.1, 10.7)	0.009
C. Study, age, sex, region only	2.3	(-0.5, 6.1)	0.64

Joint European analysis



European pooling: Contribution of each study

1. No evidence that effect of radon differed between studies

2. Influence analysis : analysis repeated by omitting each study in turn (ref Darby et al, table 10,Scan J Work Environ Health 2006, vol32 suppl 1)

   Estimated linear relationship (after stratification by study, age, sex, region of residence and smoking history) changed by less than 10% for 11 of the 13 studies

3. No significant difference
   a. when considering lung cancer diagnosis over clinical versus death certificates
   b. Study with hospital or population based studies
   c. Wether or not surrogates interviews were used
   d. Radon measurments detectors were open or closed
   e. No effect of « windows of exposure »
   f. If linear or log-linear or linear quadratic RR models were used : quite comparable results were obtained

Combined analysis from North American studies

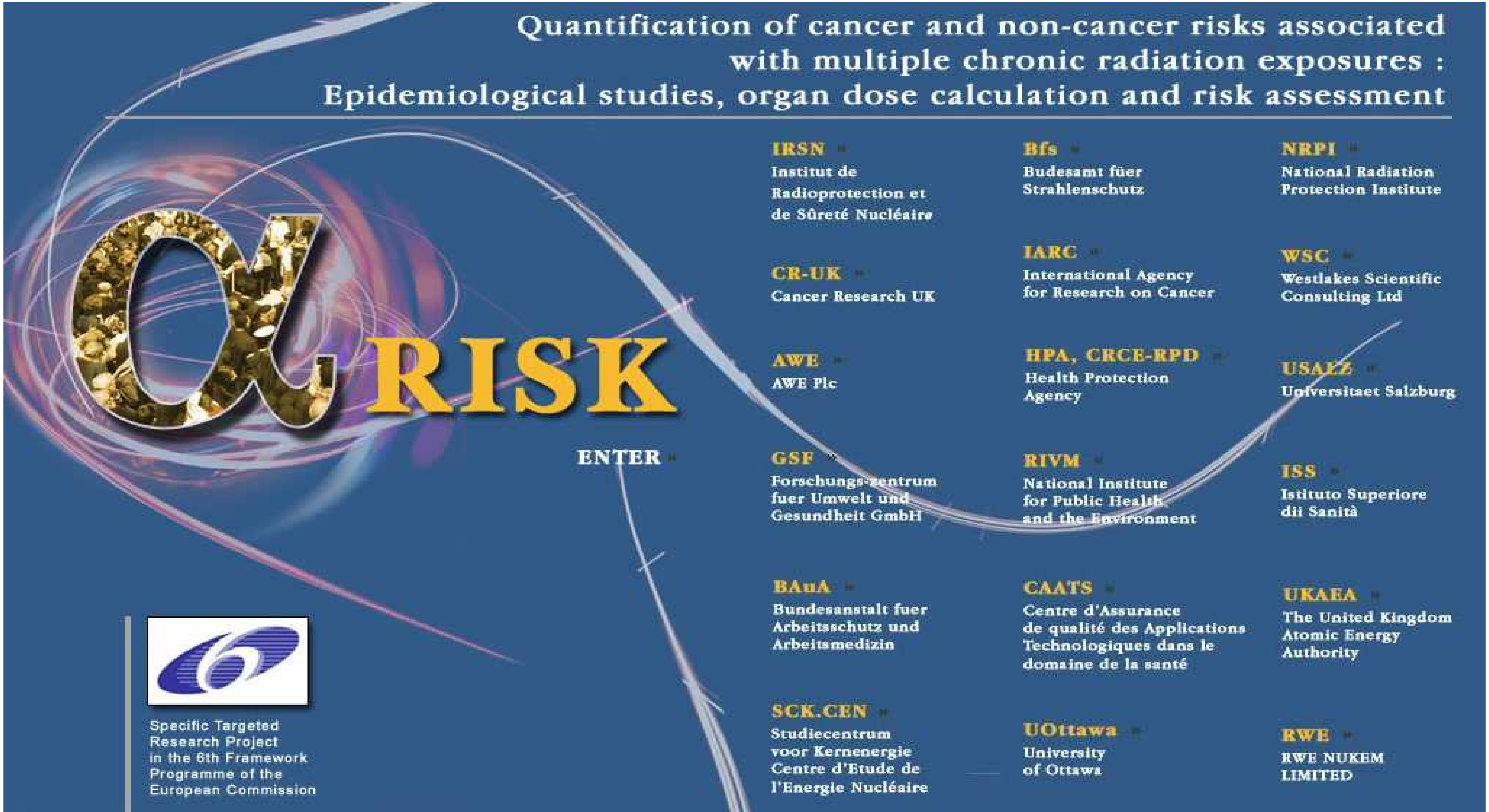
Krewski , Lubin et al, J TOX ENV H)

- **Odds ratio trend consistent with linearity (p= 0,10)**
- **Excess OR : 0,10 per 100 Bq per m^3 (CI 95 %: -0.01,0.26)**
- **If limited to residence of one or two houses and with alpha track measurments over at least 20 years :**

  EOR = 0.18 per 100 Bq per m^3 (0.02,0.43)

  Estimates are compatible with an EOR of 0.12 per 100 Bq per m^3 (0.02,0.25) predicted by extrapolation from miners studies

http://www.alpha-risk.org



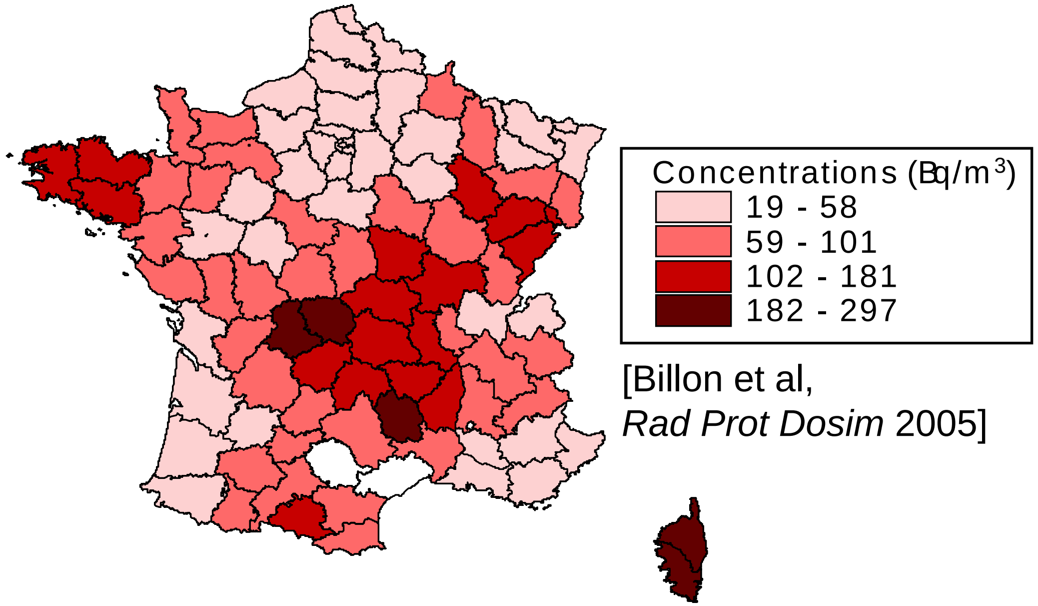
Quantitative Risk Assessment

Methodology :
Exposure–risk relationship
Models used
- European joint analysis
  [Darby et al, BMJ 2005]
- Miners studies
  [BEIR VI, 1999 ;
  Tirmarche et al, 2005]

Modifying factors
- Age at exposure
- Time since exposure
- Radon and tobacco interaction

Population data used
- national census (Insee)
- Mortality rates (Inserm)
- percentage of smokers (Insee/Credes)

Exposure data of French population
Correction of seasonal variations, type of houses, population density
- 12 261 measurments used



[Billon et al, *Rad Prot Dosim* 2005]

Quantitative Risk Assessment

25 134 lung cancer deaths in France (Inserm, 1999)

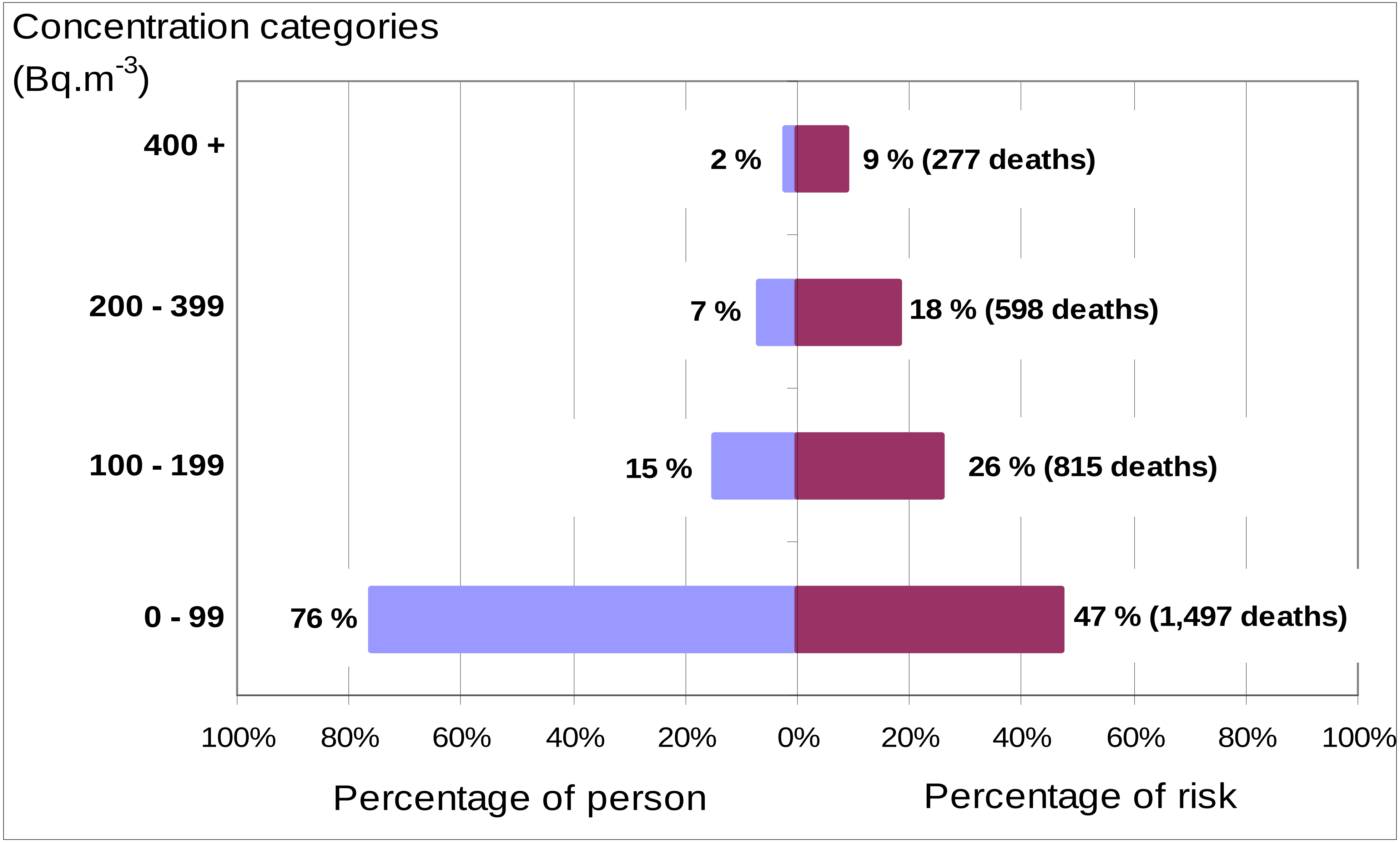
Considering the different models, uncertainty of risk coefficients and variation of radon meaurments :

> between **4,9%** (uncertainty interval at 90% : 2,4 – 9,0) and **12,3%** (11,3 – 12,8) of the Lung cancer deaths are attributable to radon in France
>
> *[Catelinois 2004]*

By taking in account interaction of tobacco-radon and percentage of smokers in France

> **75%** of cases attributable to radon are smokers

Results in France



Radon and leukemia risk

Review [Laurier, 2001]: no evidence for an association between radon exposure and leukemia

3 recent studies :

- Retrospective case-cohort study - Czech uranium miners - incidence [Rericha, 2006]
  - 84 leukemia cases (53 CLL)
  - leukemia risk associated with cumulative radon exposure
  - CLL risk associated with cumulative radon exposure

- Cohort study - Czech uranium miners – mortality [Tomasek, 2006]
  - 30 deaths from leukemia
  - risk increased with duration of work
  - risk not significantly associated with cumulative radon exposure
  - calculation of equivalent RBM dose : LLRn > 60%, radon < 10%
  - risk of leukemia associated with cumulated equivalent RBM dose

- Case-control study - Former uranium miners, East Germany - incidence [Mohner, 2006]
  - 377 leukemia cases and 980 controls
  - elevated risk for employees with a very long duration of work
  - calculation of equivalent RBM dose : radon > 75%
  - no association with exposure to short-lived radon progeny

Radon and leukemia risk

- some evidence of an increased risk of leukemia among miners
- increased risk associated with a long duration of exposure
- association with cumulative radon exposure not yet confirmed
- need for considering the different components of exposure (radon, gamma, LLRn)
- need for considering the uncertainties in exposure and dose assessment

Radon and childhood leukemia in France (1990-2001)

ref PhD 2006: Envir. exp. to radiation and childhood leukemia , AS Evrard and Health Physics 2006

A signifcant positive association between indoor radon and AML incidence, remained significant in multivariate analysis, including either terrestrial gamma dose or total gamma dose

	<35 Bq/m^3	35-46 Bq/m^3	48-61 Bq/m^3	61-92 Bq/m^3	>-93 Bq/m^3
All acute leuk. (O/exp)	1 (1055/1100,9)	1.01 (1042/1080,8)	1.05 (1084/1079,3)	1.11 (1086/1022,2)	1.06 (1063/1046,7)
ALL (0/exp)	1 (860/896,8)	1,00 (848/881,7)	1,07 (906/880,6)	1,12 (895/833,6)	1,02 (837/853,2)
AML (O/exp)	1 (183/189.1)	1,01 (181/184,6)	0,9 (161/184,1)	1,06 (179/174,8)	1,20 (208/179,4)

Radon and childhood leukemia in France (1990-2001)

ref PhD 2006: Envir. exp. to radiation and childhood leukemia , AS Evrard and Health Physics 2006

1. Association with AML seems limited to those less then 14 years old
2. After adjustement on rural areas, proportion of managers, proportion of university graduates, average net income :

➔ association between radon and childhood leukemia persists
SIR is multiplied by 1.20 for 100 Bq/m^3 increase

UK Childhood Cancer Study : domestic radon exposure (ref BJC(2002)86)

No evidence of increased risk in relation to domestic radon

Radon concentrations considered were close to time of diagnosis : 2226 cases and 3773 control homes

- But houses of controls have intrinsic features resulting in higher than average indoor radon concentrations.
- If radiation risk estimates (Com. Medical Aspects of Radiation in Env.) suggests that approximately 14% of leukemia incidence in childhood in UK may be linked to natural background radiation, what is the power of a case-control study to demonstrate clearly this excess ?
- Number of cases in high exposed regions may be too small ?
- Adjustment on co-factors ? Yet unknown

Radon and diseases other than cancer

1. Cardiovascular diseases :
   a. large Wismuth study: no increase of risk with radon exposure
   b. New Foundland study : suggested an increase, not confirmed in a recent publication
2. Multiple sclerosis, Alzheimer :
   a. Ecological study in Norway (Bolviken, 2003)
   b. Cluster in a specific part of the country, co-relation with radon or other geochemical caracteristics ?
3. Conclusion : at present no evidence of a clear link

Radon in homes and cancer: Conclusion

1. Clear evidence of lung cancer risk

a. Calculation of attributable risk does not mean that we are able to reduce all of those theoretically estimated diseases
b. Interaction between radon and tobacco should be studied further
c. Risk managment is possible without converting in mSv

2. Leukemia : no clear evidence to-day,

a. but further survey and studies necessary
b. calculation of RBM dose, Uminers studies, other studies ?
c. mechanism, different for induction in childhood or exposure in adults ?
d. animal data : not in favour of a leukemia risk linked to radon
e. radon gas or WLM
f. Other cofactor, unknown

ICRP C1 Task group an cancer risk in relation to alpha emitters

4 years program :

Radon, thorotrast, plutonium, uranium

Discussion of convincing evidence from epidemiological studies, low dose risk, dosimetric component, contribution by ICRP C2 members, evidence from animal experiments…..

Special mandate for a radon statement during next six months : close to risk management approach (contribution by C4)