

**IRSN**

INSTITUT  
DE RADIOPROTECTION  
ET DE SÛRETÉ NUCLÉAIRE

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

Recent Research programs  
Implications for risk management

Margot Tirmarche

IRSN-FRANCE

Coordinator of European programs

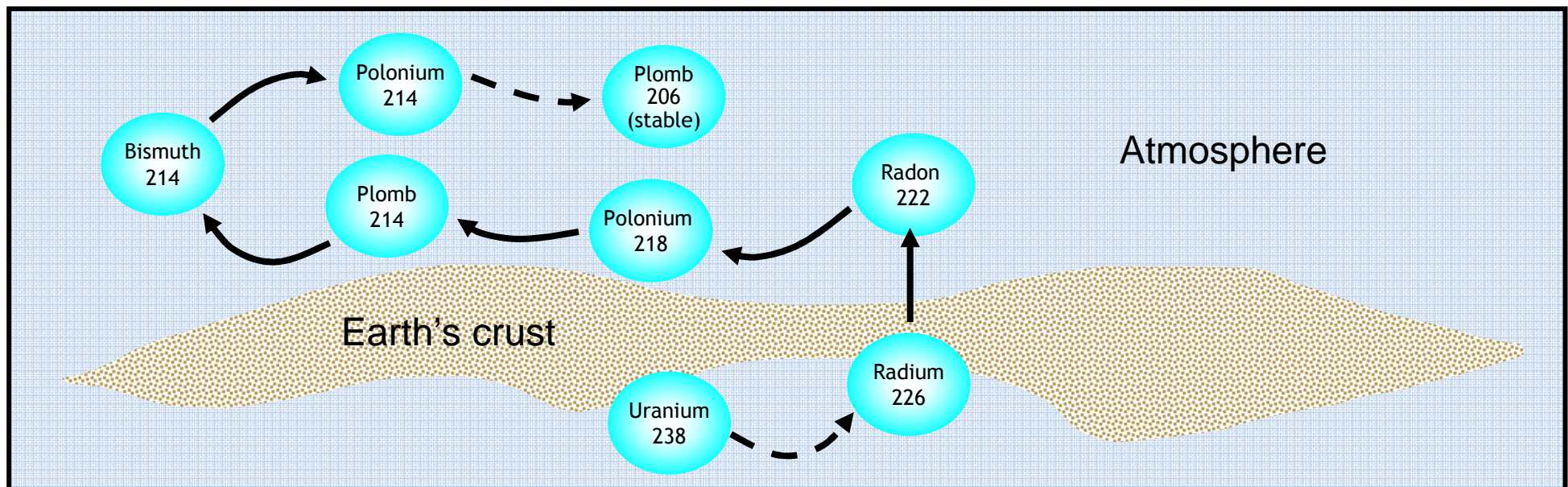
In charge of ICRP C1 Task Group 64 « Cancer risk from alpha emitters »

# Radon-222

A naturally occurring gas, arises from decay chain of Uranium-238 present in the earth crust. Is present in our daily environment, but still ignored by many persons.

If inhaled, radon is exhaled rapidly, but its short lived decay products may be deposited at bronchial epithelium level and cells be exposed to alpha radiation.

Since 1988 (IARC) radon is a well recognized lung carcinogen for humans : based on results from miners and experimental studies



# 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 »

2008

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

2009

Statement by ICRP and Handbook of WHO

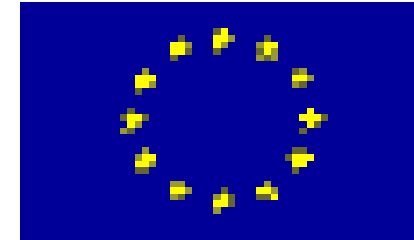
# The “Uminers + Animal data” European project

## 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](http://www.irsn.org)



# The Alpha-risk European project

Specific targeted research or innovation project (STREP)

Contract no. 516483 (FI6R)

Duration: July 2005 – June 2009

Coordinator: M Tirmarche (IRSN)



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](http://www.alpharisk.org)

Epidemiology during last 15 years :

Is radon inducing cancer at low daily exposure ?

Which approach ?  
Which implications ?

1. Descriptive studies, also called ecological studies

2. Analytical studies :

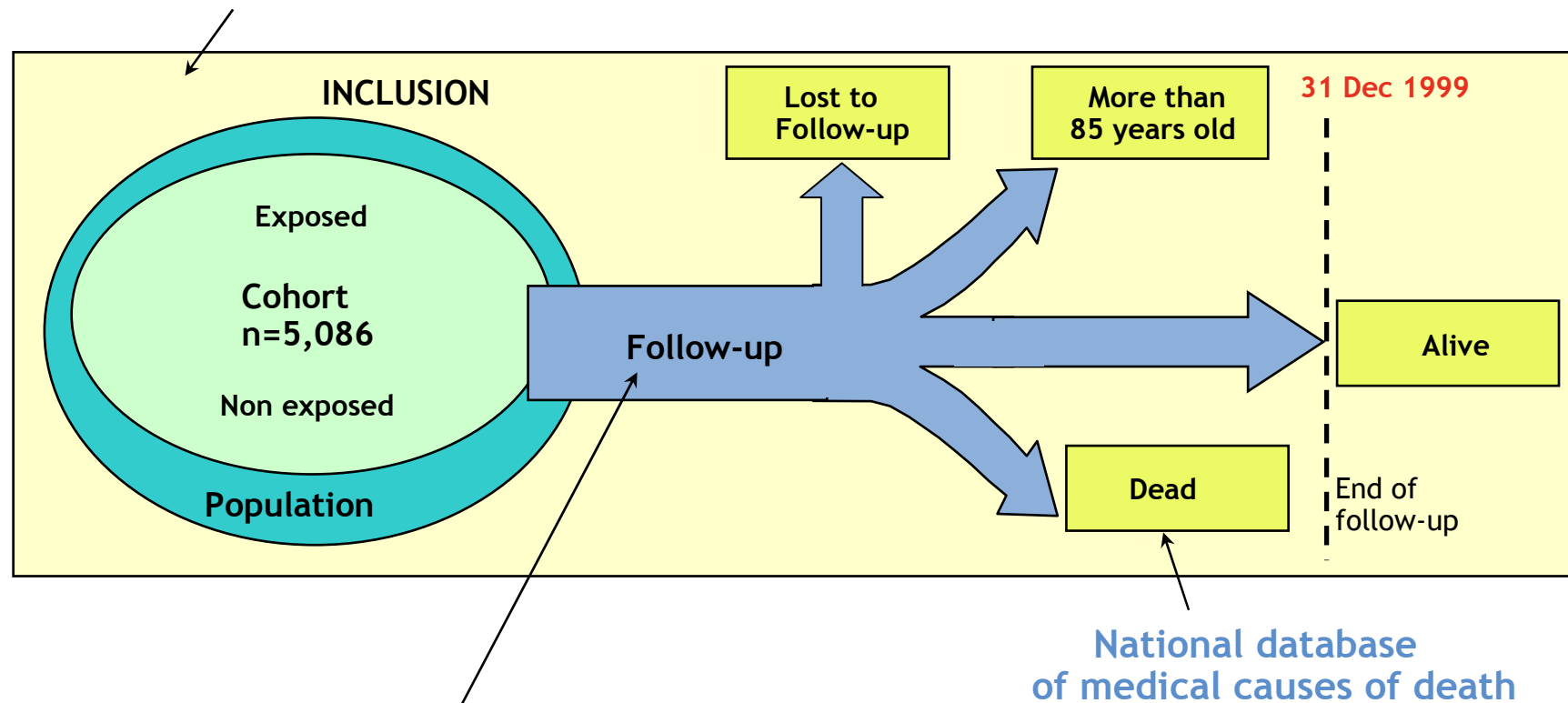
- a. either cohort studies, example : follow-up of uranium miners
- b. or case control studies, example : lung cancer risk linked to domestic exposure

3. Quantitative risk assessment

# PROTOCOL

Example French miner cohort :

Criteria of inclusion : Employed at least 1 year between 1946 and 1990



Vital status: matching with the national database of individual identification

Exposure: historical reconstruction from 1946 to 1955, and individual records afterward

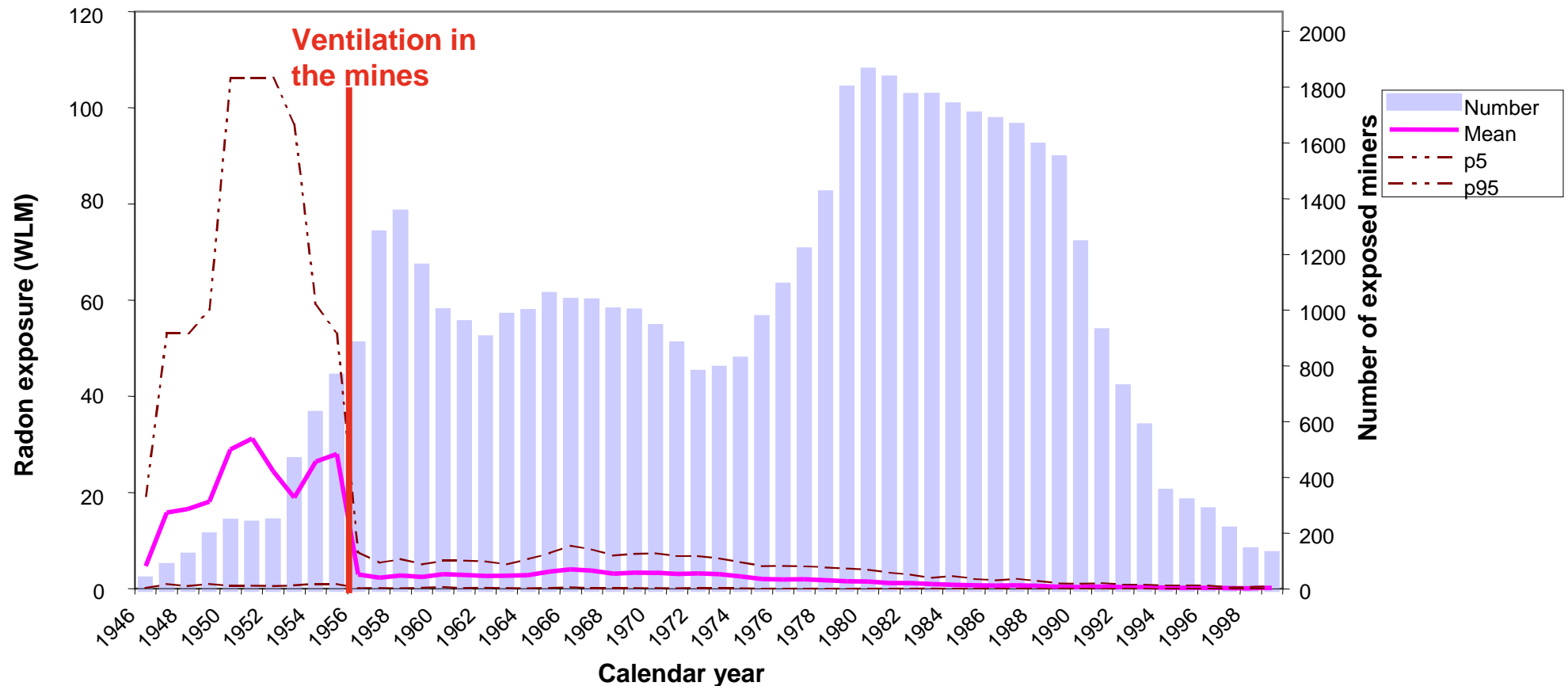
# RESULTS: Characteristics of the cohort

Follow-up to 1999

Number of miners	5,086
Person-years	153,063
Mean age at study start (Min - Max)	28.8 (16 - 69)
Mean duration of follow-up (Min - Max)	30.1 (0.1 - 53.6)
Mean age at study end (Min - Max)	58.9 (19 - 85)
Number of deaths (%)	1,467 (29)
Number of lost to follow-up (%)	66 (1)

# DISTRIBUTION OF RADON EXPOSURE

Distribution of yearly radon exposure (WLM)  
among the French cohort of uranium miners 1946-1999



- Unit of radon exposure: Working Level Month (WLM)

# RESULTS: Characteristics of the exposure

Follow-up to 1999

Number of exposed miners (%)

4 132 (81)

Mean cumulative radon exposure WLM (Min-Max)

36.6 (<1 - 960)

Mean duration of radon exposure ( Min - Max)

13.1 (1 - 35)

Mean age at first exposure (Min - Max)

29.1 (15 - 63)

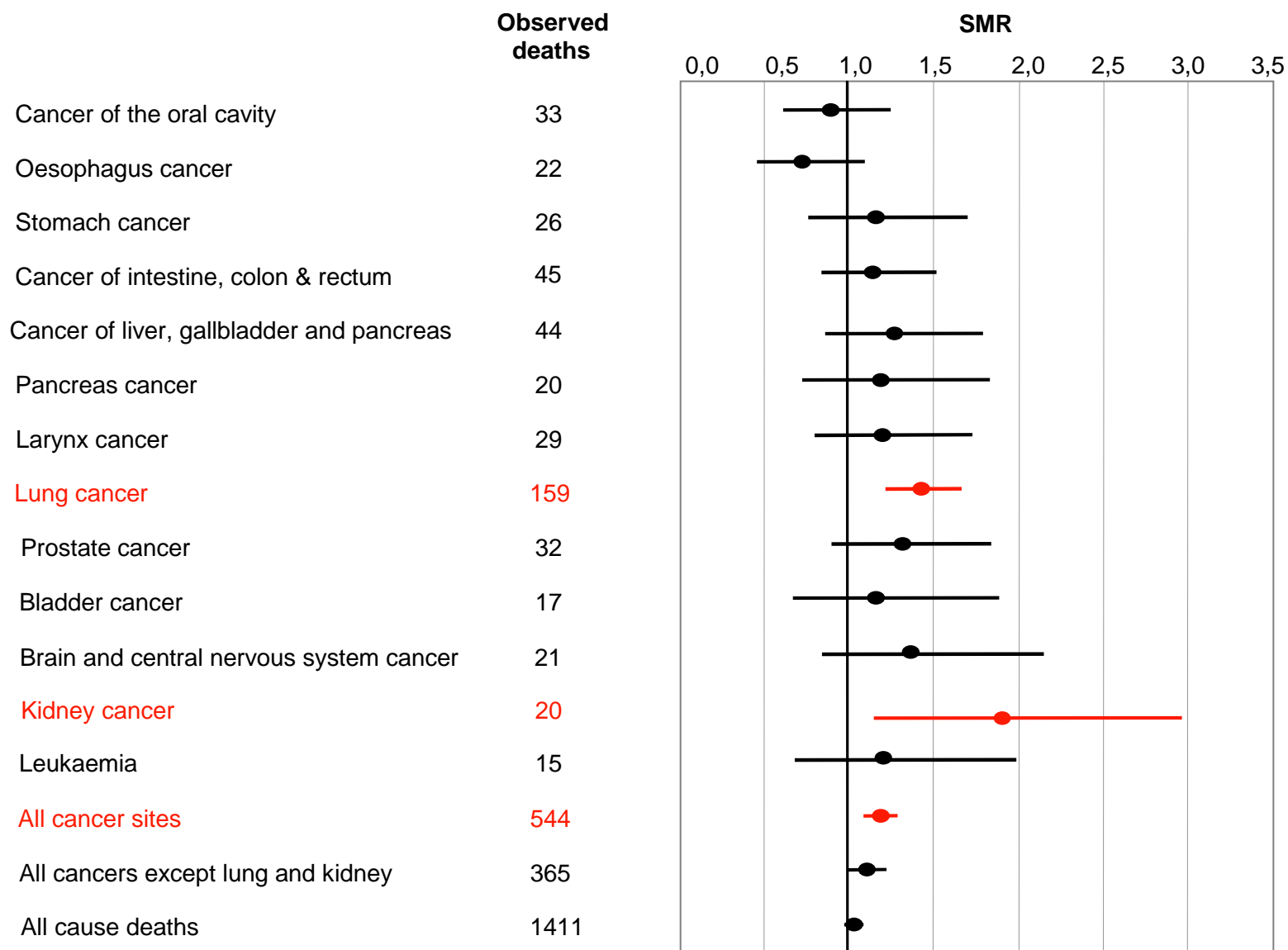
Mean age at last exposure (Min - Max)

41.1 (16 - 64)

# RESULTS: Mortality risk

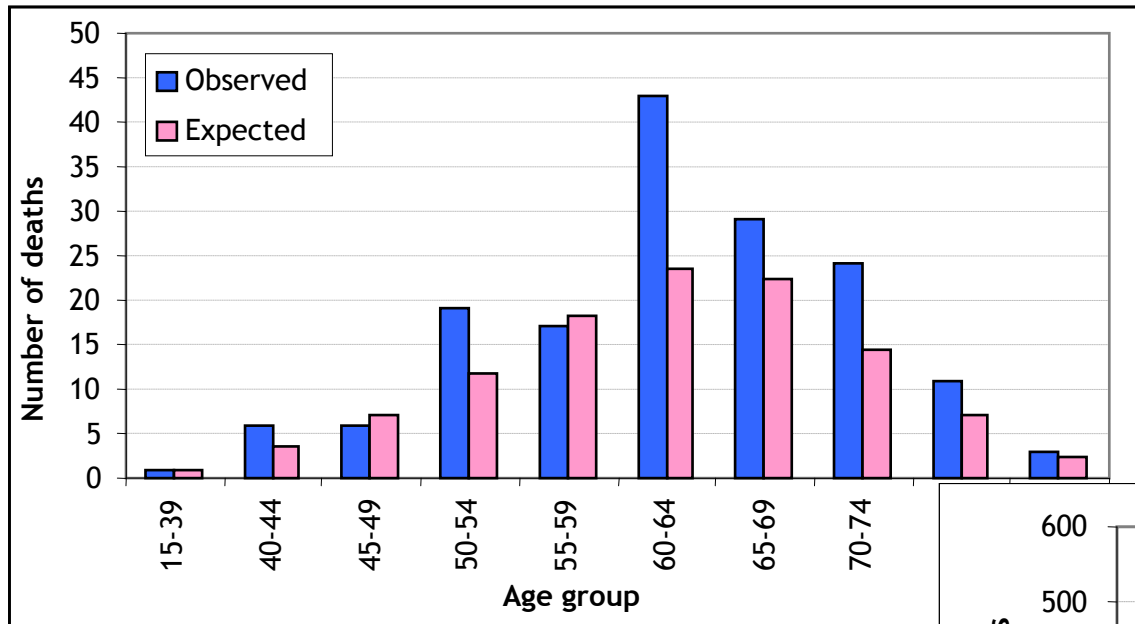
Causes	Observed	SMR	95% CI
ALL CAUSES	1,404	1.0	1.0 - 1.1
ALL CANCERS	544	1.2	1.1 - 1.3
NON CANCER	867	0.9	0.9 - 1.0
NERVOUS SYSTEM	24	1.1	0.7 - 1.6
CIRCULATORY SYSTEM	319	1.0	0.9 - 1.2
RESPIRATORY SYSTEM	80	1.3	1.0 - 1.6
SILICOSIS	23	7.1	4.5 - 10.7
RESPIRATORY SYSTEM (except SILICOSIS)	57	1.0	0.7 - 1.3
DIGESTIVE SYSTEM	101	1.0	0.8 - 1.2
EXTERNAL CAUSES	196	1.1	0.9 - 1.2

# RESULTS: Mortality risk by cancer site

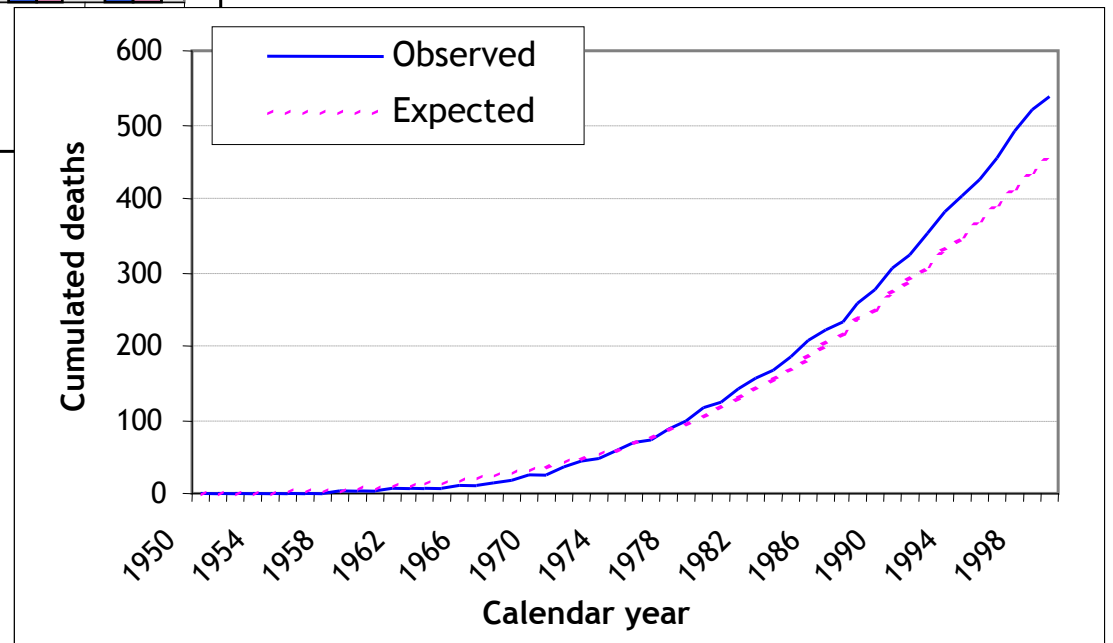


● Standardised Mortality ratio (SMR) — 95% Confidence interval

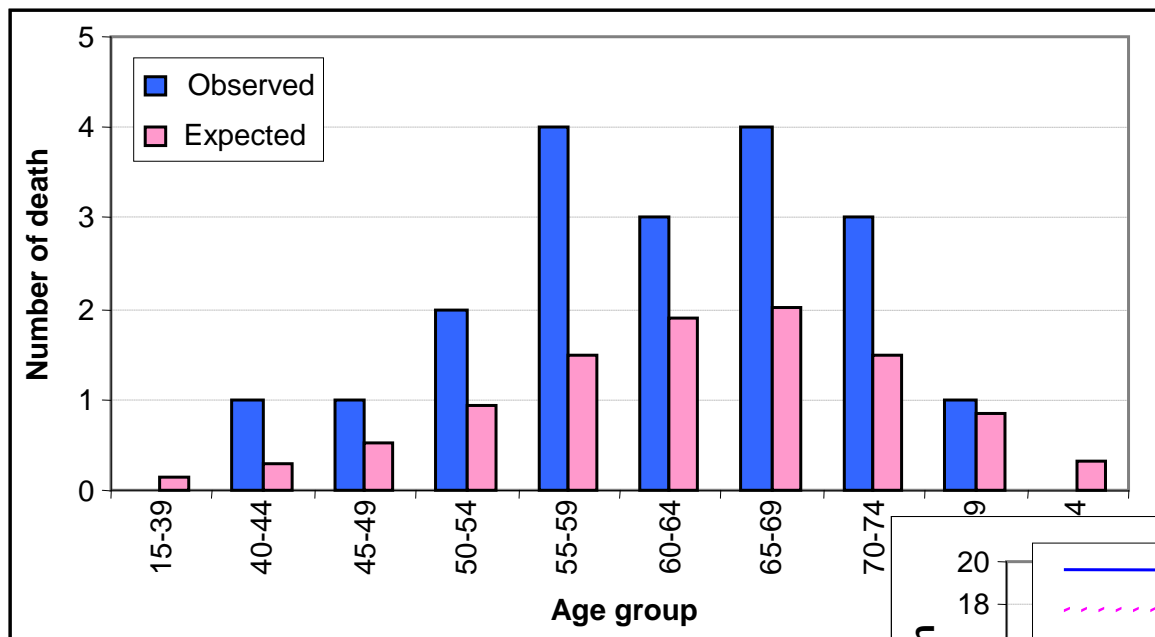
# RESULTS: Lung cancer mortality



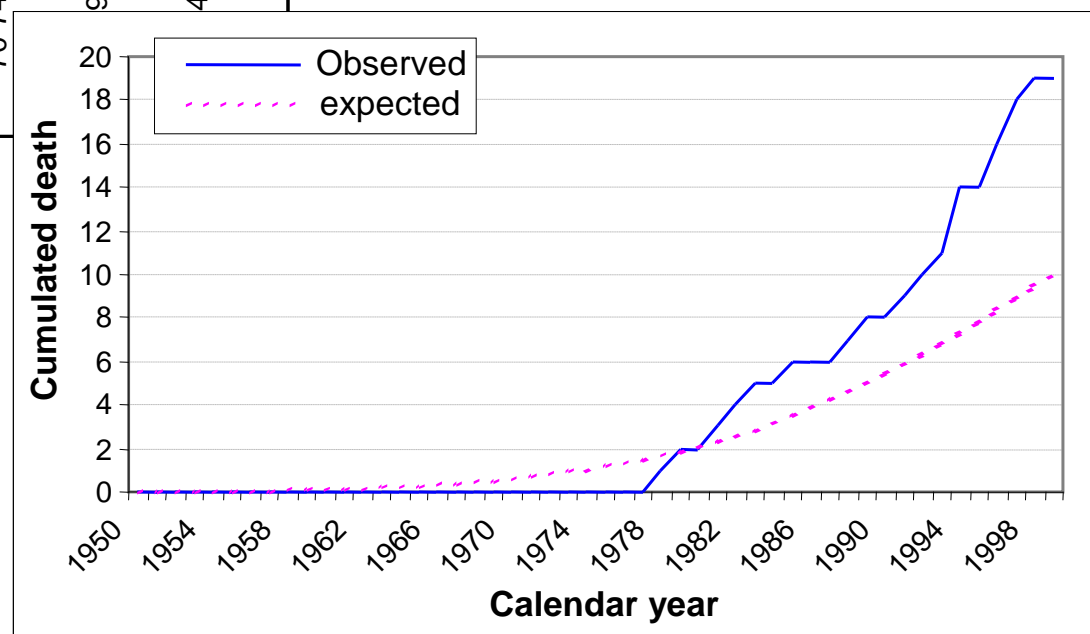
O = 159 ; E = 111.5  
SMR = 1.43 [1.21 ; 1.67]



# RESULTS: Kidney cancer mortality

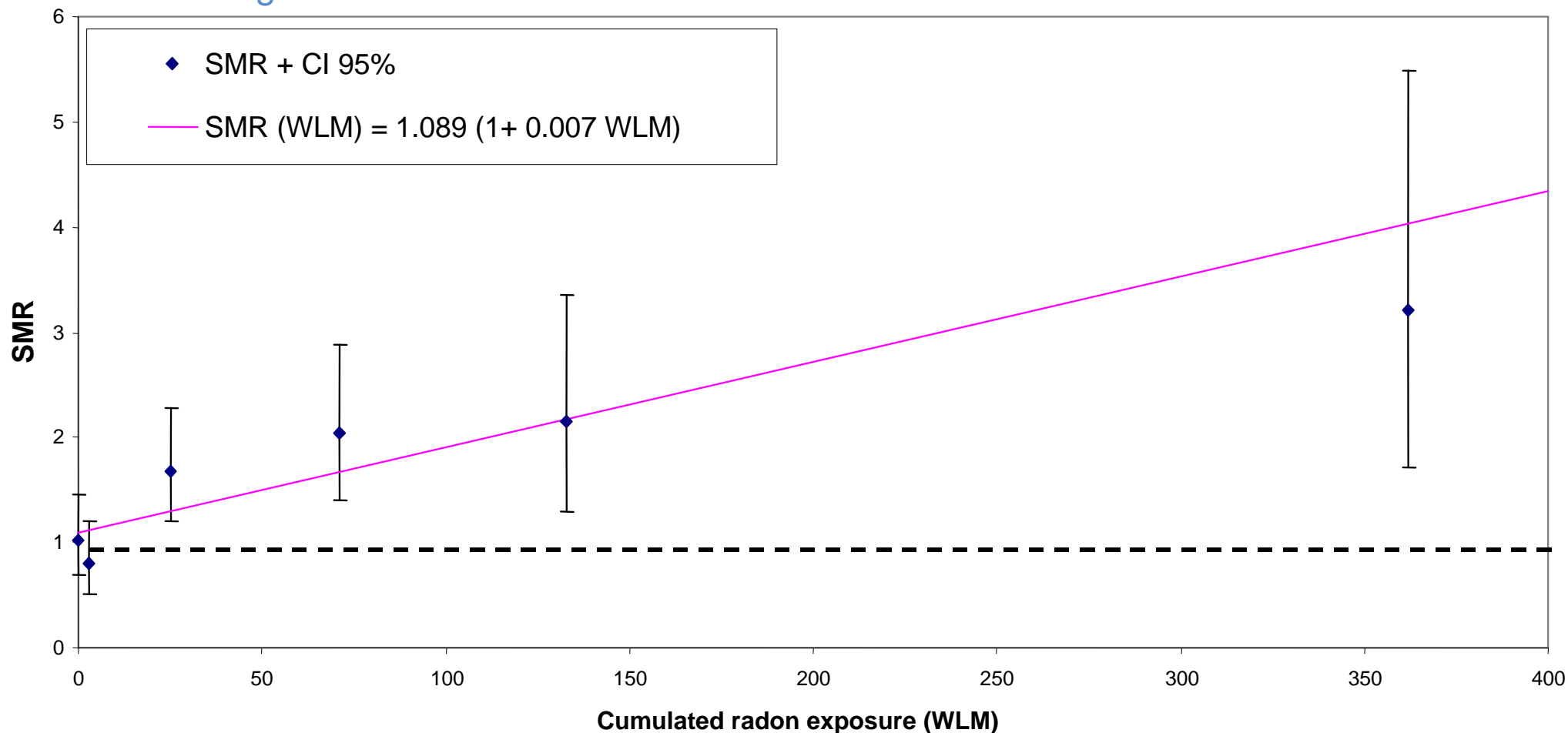


O = 20 ; A = 10,0  
SMR = 2,00 [1,22 ; 3,09]



# RESULTS: Lung cancer risk and radon exposure

## External regression





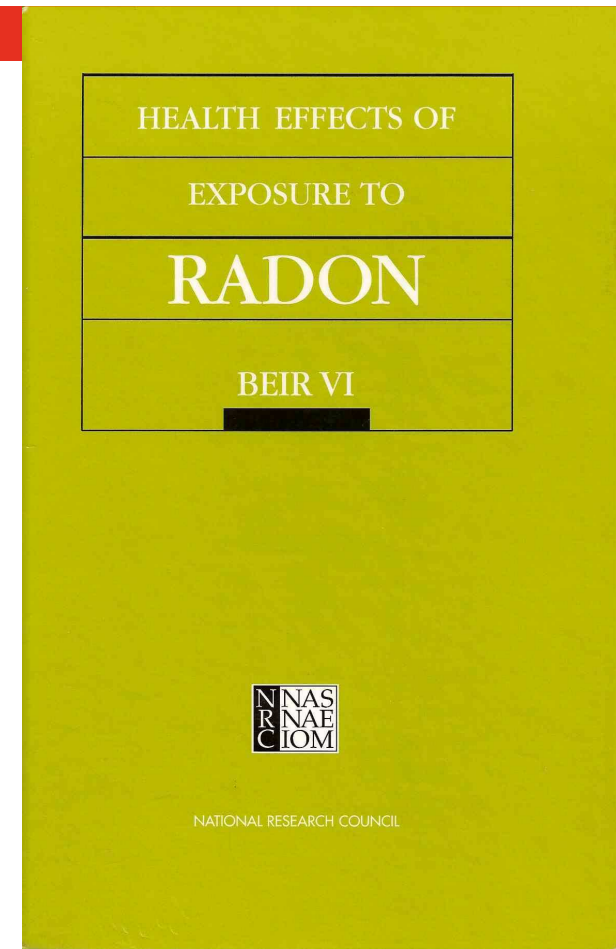
# BEIR VI Report

## 11 cohorts

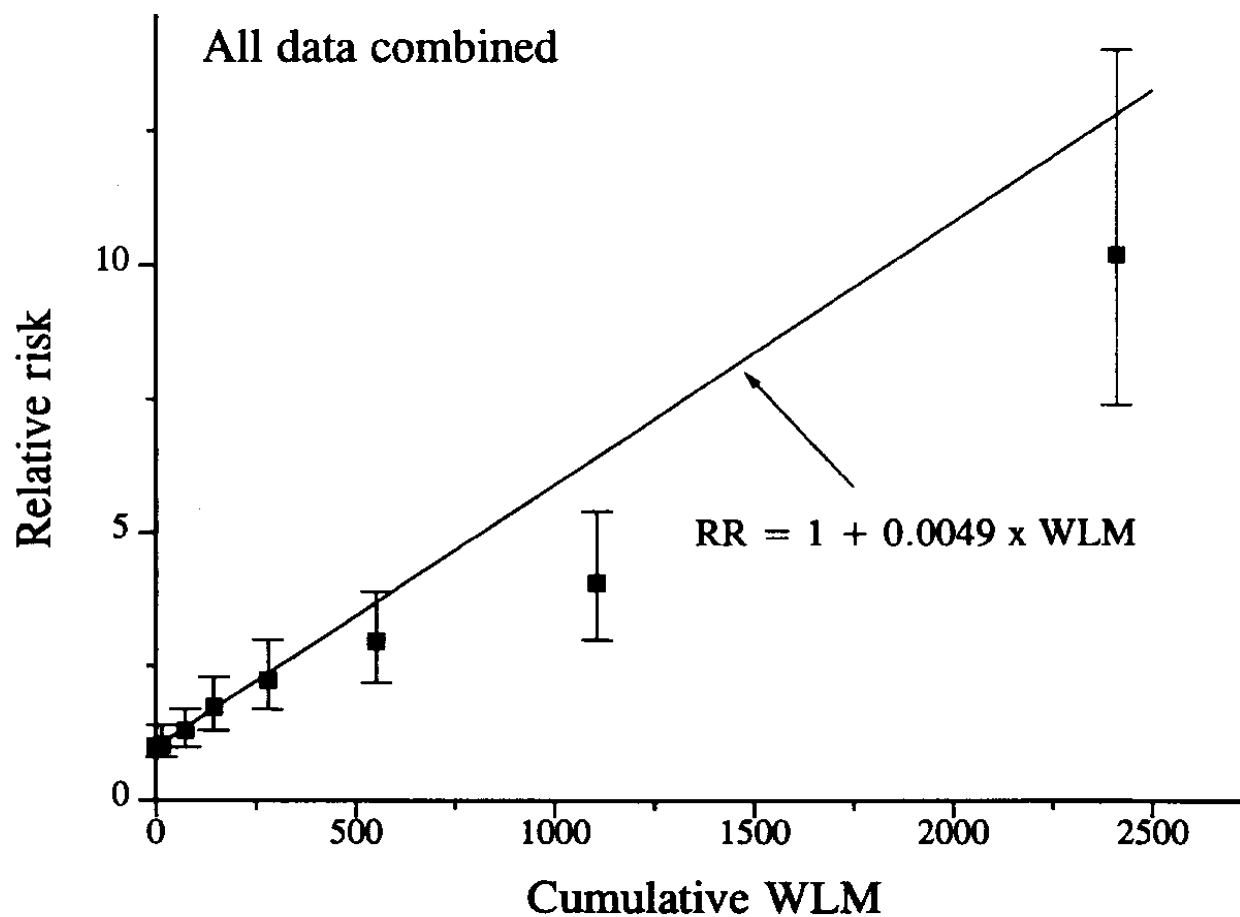
- > 60000 miners
- > 2600 lung cancer deaths

## Results

- ERR/100 WLM 0.49 [0.2 – 1.0]
- Agreement with a linear model
- ERR  $\searrow$  with Time Since Exposure
- ERR  $\searrow$  with Age at Exposure
- inverse exposure rate effect
- sub-multiplicative 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 (years)	
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)

# Points of research and objectives on European level

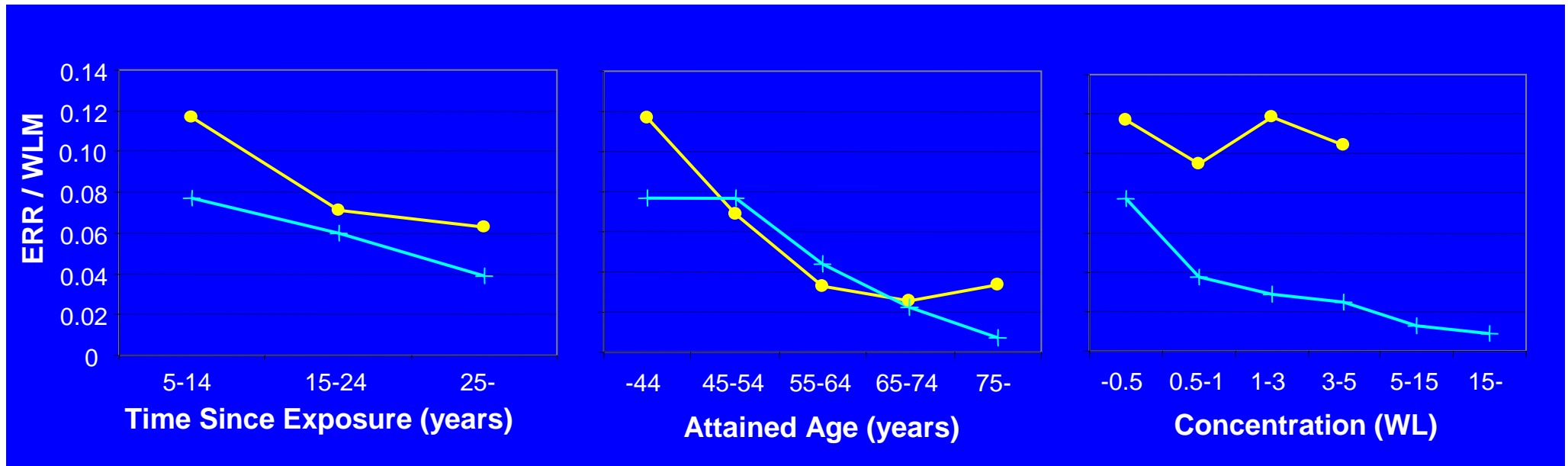
Extended follow-up and new cohorts :

- 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

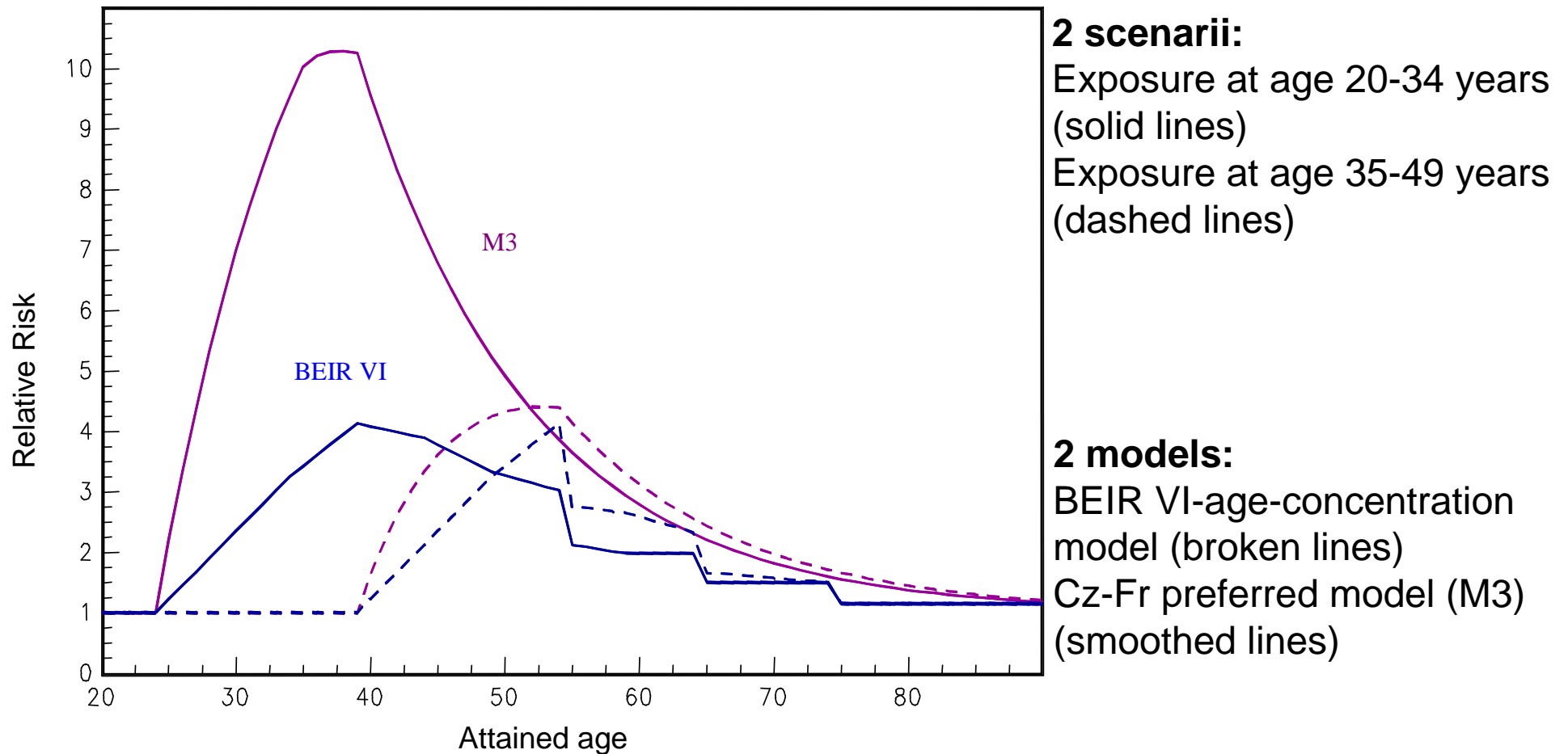


<span style="color: yellow;">●</span> <b>Cz+Fr</b>	10 100 miners – 573 lung cancer deaths – 95% of exposure years at rate < 2 WL
<span style="color: cyan;">+</span> <b>BEIR 6</b>	11 cohorts of miners – 2787 lung cancer deaths – dose rate up to > 15 WL

**➔** 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)



[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. Risk of lung cancer :

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

## 2. Leukemia risk ?

- a. Studies in adults, in childhood leukemia

# Radon risk at low annual exposure in houses ?

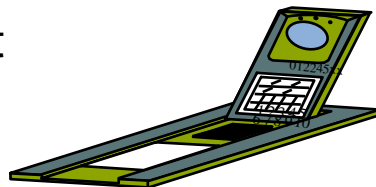
Gas : concentration is depending of underground characteristics, changes on geographical level,

seasonal corrections are needed

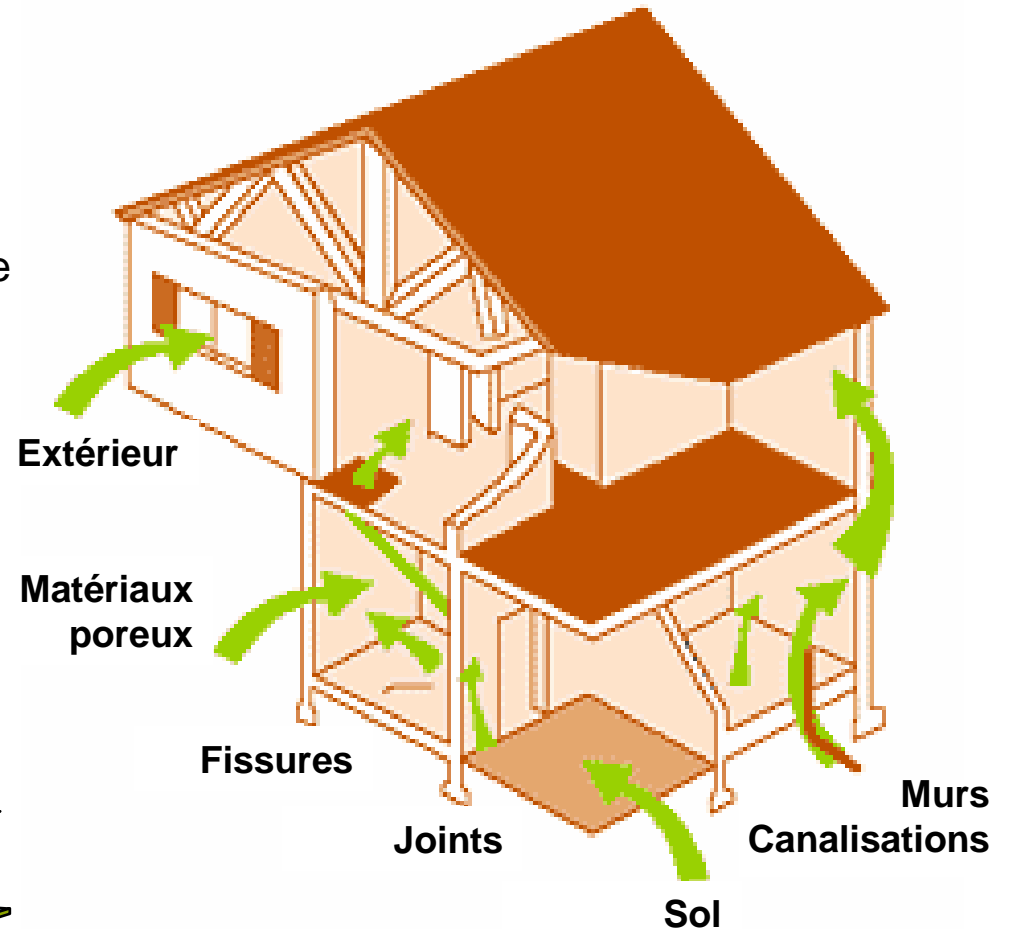
Habits of live should be taken in account, residence level...

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

→ Individual measurement 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<sup>-3</sup>** CI 95% = [0.99 – 1.11]

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

**RR = 1.07 per 100 Bq.m<sup>-3</sup>** CI 95% = [1.00 – 1.15]

(if limited to those with all houses measured)

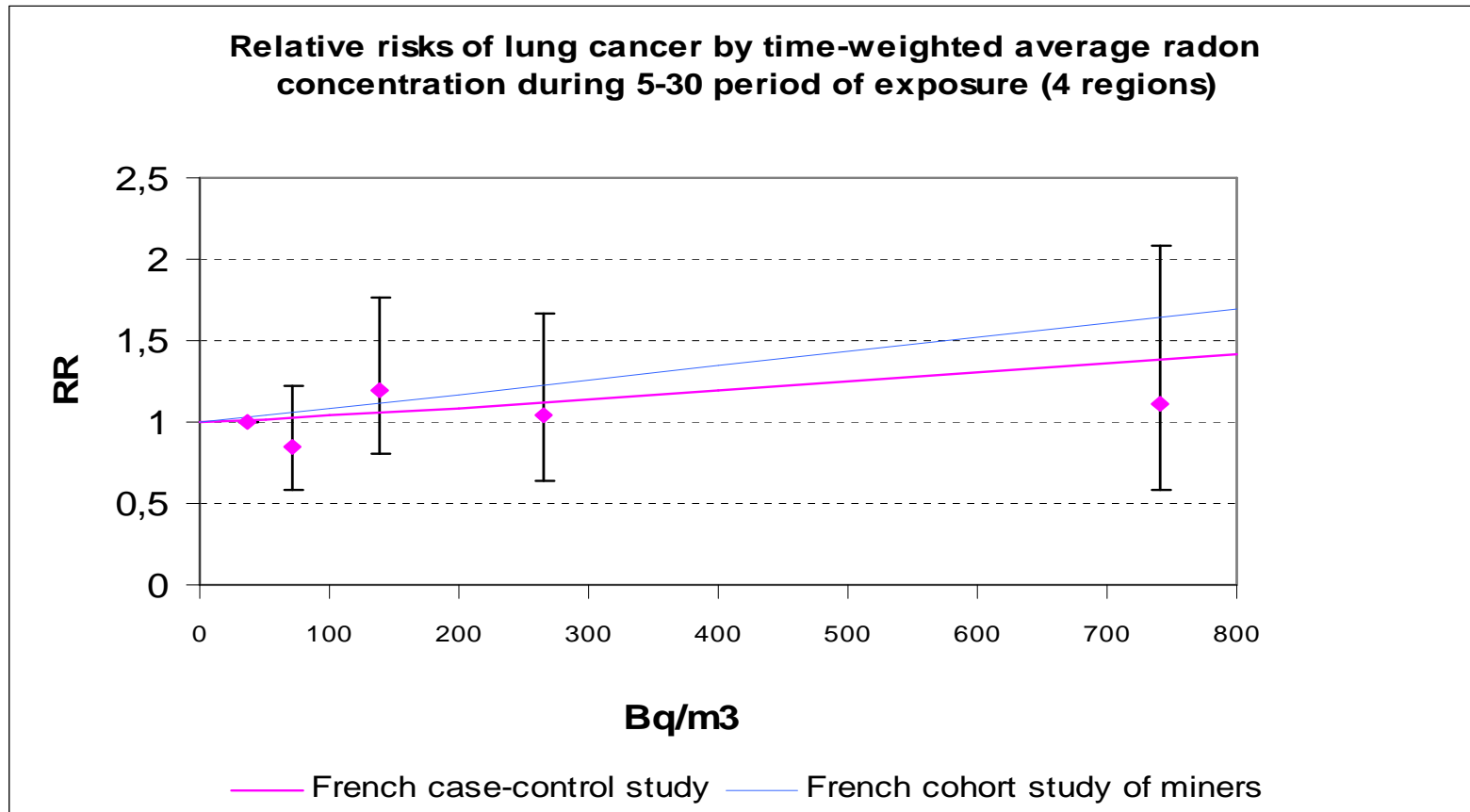
- This risk is low when compared to the risk associated to smoking
- This result is concordant with those from previous studies and with the risk extrapolated from miners studies

- 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<sup>3</sup>

25 WLM  $\leftrightarrow$  230 Bq/m<sup>3</sup> for 25 years  
 $\Rightarrow$  RR=1.008 per WLM  
 $\Rightarrow$  RR=1.09 per 100 Bq/m<sup>3</sup>

# 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<sup>3</sup> 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) and 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 measurements, 7 148 cas / 14 208 témoins

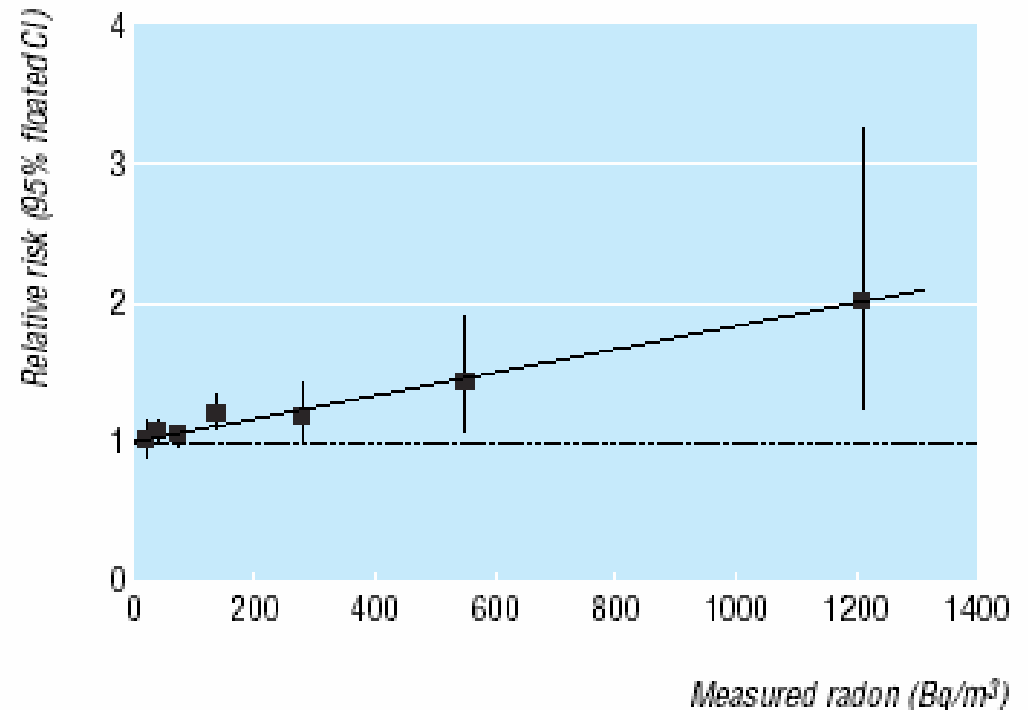
## • Results : linear dose-response relationship

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

$$RR = 1,08 \text{ for } 100 \text{ Bq/m}^3 \quad [1,03 - 1,16]$$

➔ Significant relationship if limited to those exposed  $\leq 200 \text{ Bq/m}^3$

Significant increase for nonsmokers



[Darby et al, *BMJ* 2005]

## EUROPEAN POOLING Study : non-smokers

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

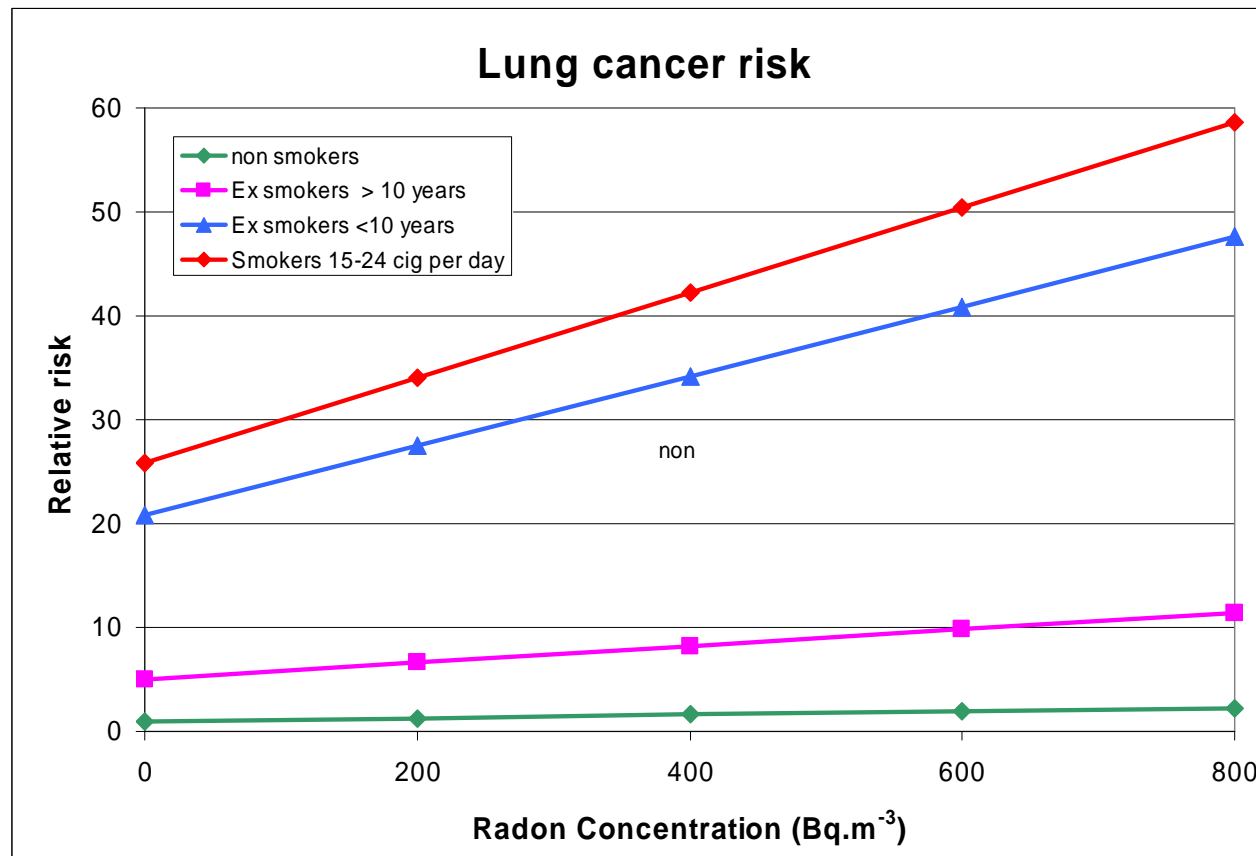
Percentages calculated after stratification for study, age, sex, and region of residence

## EUROPEAN POOLING Study :

### Effect of stratification for smoking

Stratification	% increase in lung cancer risk per 100 Bq/m <sup>3</sup> 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. Whether or not surrogates interviews were used
- d. Radon measurements 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 measurements 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>

Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures :  
Epidemiological studies, organ dose calculation and risk assessment



**ENTER**

<b>IRSN</b> « Institut de Radioprotection et de Sûreté Nucléaire	<b>Bfs</b> « Bundesamt für Strahlenschutz	<b>NRPI</b> « National Radiation Protection Institute
<b>CR-UK</b> « Cancer Research UK	<b>IARC</b> « International Agency for Research on Cancer	<b>WSC</b> « Westlakes Scientific Consulting Ltd
<b>AWE</b> « AWE Plc	<b>HPA, CRCE-RPD</b> « Health Protection Agency	<b>USAZS</b> « Universität Salzburg
<b>GSF</b> « Forschungszentrum für Umwelt und Gesundheit GmbH	<b>RIVM</b> « National Institute for Public Health and the Environment	<b>ISS</b> « Istituto Superiore di Sanità
<b>BAuA</b> « Bundesanstalt für Arbeitsschutz und Arbeitsmedizin	<b>CAATS</b> « Centre d'Assurance de qualité des Applications Technologiques dans le domaine de la santé	<b>UKAEA</b> « The United Kingdom Atomic Energy Authority
<b>SCK.CEN</b> « Studiecentrum voor Kernenergie Centre d'Etude de l'Energie Nucléaire	<b>UOttawa</b> « University of Ottawa	<b>RWE</b> « RWE NUKEM LIMITED



Specific Targeted Research Project in the 6th Framework Programme of the European Commission

# 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<sup>3</sup>

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 ?

# 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

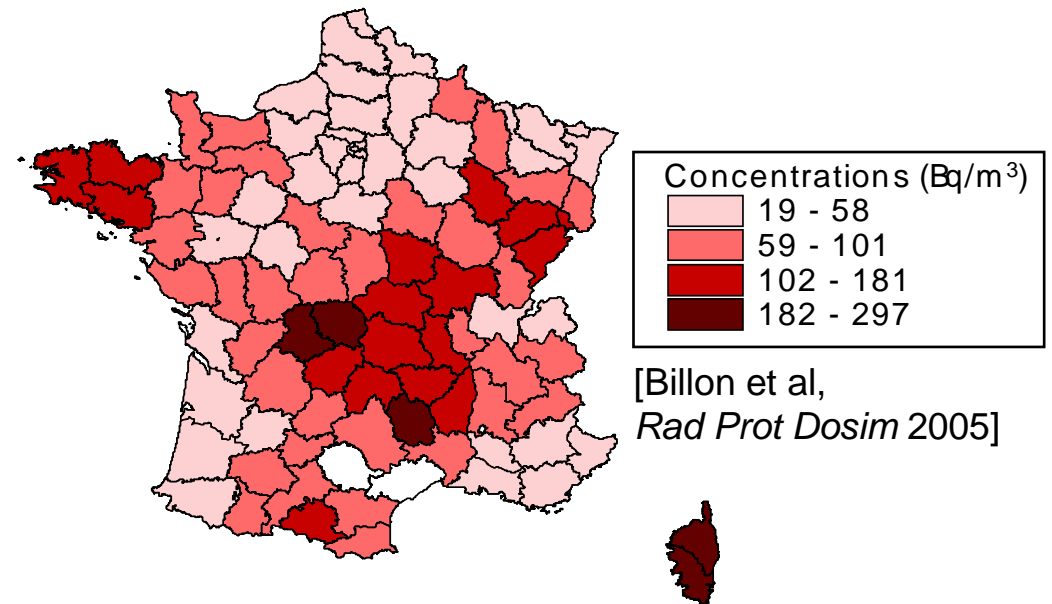
### Population data used

- 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 measurements used



# Quantitative Risk Assessment

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

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

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]*

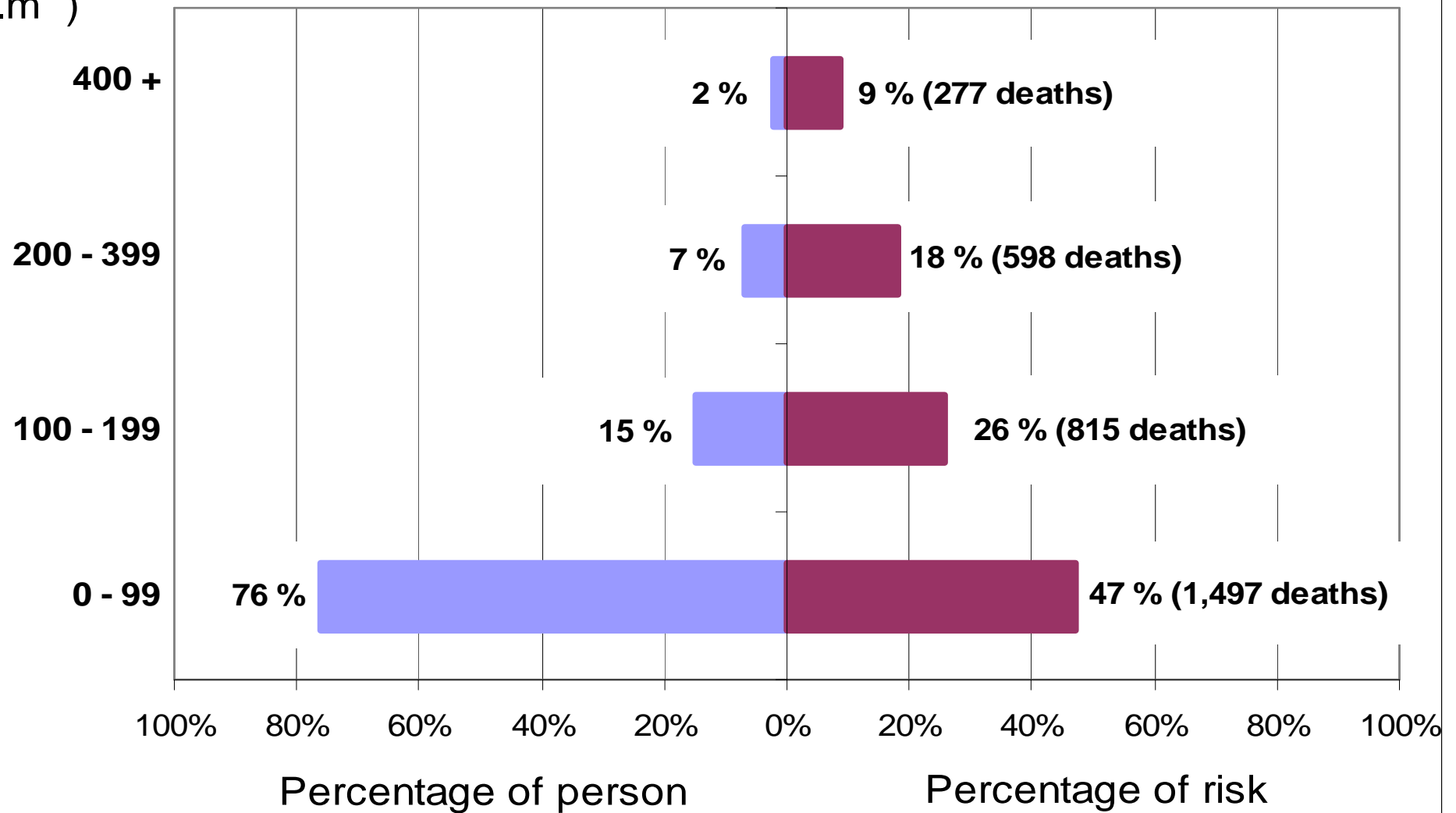
By taking in account interaction of tobacco-radon and percentage of smokers in France

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

# Results in France

Concentration categories

(Bq.m<sup>-3</sup>)



# 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]

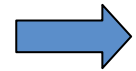
377 leukemia cases and 980 controls

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 significant 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 <sup>3</sup>	35-46 Bq/m <sup>3</sup>	48-61 Bq/m <sup>3</sup>	61-92 Bq/m <sup>3</sup>	>-93 Bq/m <sup>3</sup>
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 (O/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 than 14 years old
2. After adjustment 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<sup>3</sup> 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 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 management 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 on cancer risk in relation to alpha emitters

4 years program :

Radon, thorostrast, 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 :**

if considering updated risk coefficient from Eu miners data and pooled analysis from domestic studies and

if using the *Dose conversion convention as presented under ICRP65* ,

→ ICRP proposal is to revise the correspondence based on equivalence with 10 mSv ( draft report presently under discussion).