IRSN
INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

Lung cancer risk from radon and radon progeny.

Epidemiological studies

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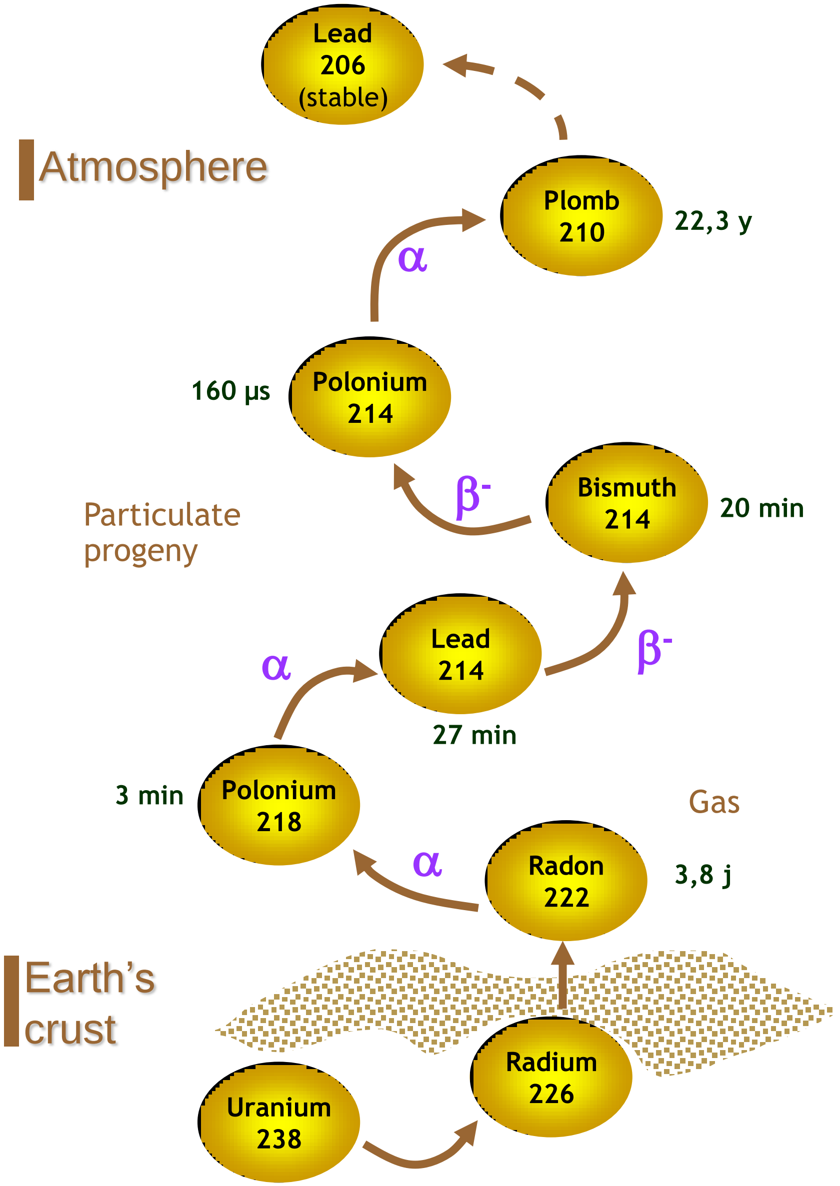
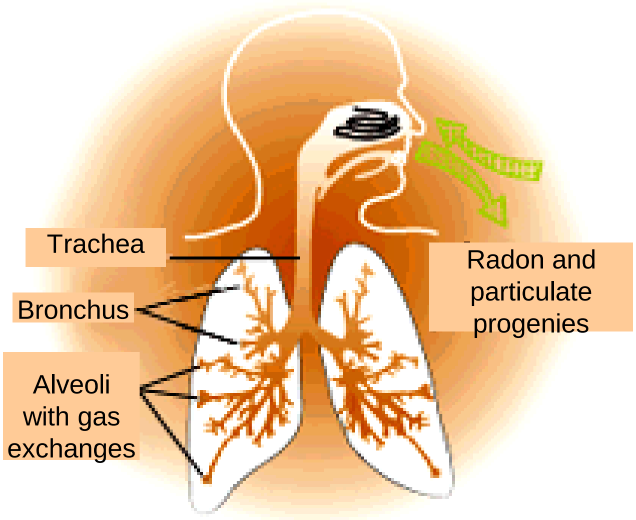
↗ What about radon ?

- Radon is a **radioactive gas of natural** origin
- It comes from the disintegration of uranium from the soil
- It is present **everywhere** at the surface of the earth
- It is colorless and odorless
- It concentrates in **confined places**
- It is a emitter of α **particles**
- **Chronic exposure**, over the life span, for the **whole population**



↗ Mechanisms of action



- Inhalation of radon
  - Internal exposure to radon and its short-lived progeny
- Distribution of radionuclides in the whole body, mainly in the lungs → irradiation of bronchial epithelium due to radon progenies
- Dosimetric models show that :
  - > 90 % of the received dose is delivered to the lung
  - Dose delivered to the other organs ≈ 100 fold lower
  - But a part of this dose can be delivered to the red bone marrow (organ at risk for leukemia)
- In 1988, the International Agency for Research on Cancer (CIRC-OMS) classified radon as a known pulmonary carcinogen in humans
  - Experimental studies in vivo and in vitro: inhalation of radon for three species of animals (rats, hamsters and dogs)
  - Results from epidemiological studies among miners (uranium, tin, fluorspar)

↗ Historic of knowledge

1567	Unusual mortality from respiratory diseases among young miners (*Mala Metallorum*, Paracelse)
1879	Diseases identified as cancer of bronchus
1898	Discovery of radium (Curie)
1924	First mention as occupational disease
1940	Inhalation of radon presented as possible (Planck)
1946	Beginning of intensive extraction of uranium in France
1956	First measures of radioprotection in France
1960	Launch of the first **epidemiological studies among miners**
1988	Radon classified as a known pulmonary carcinogen in humans
1990	Launch of the first **epidemiological studies in general population**

Epidemiological studies among uranium miners

↗ Studies among miners

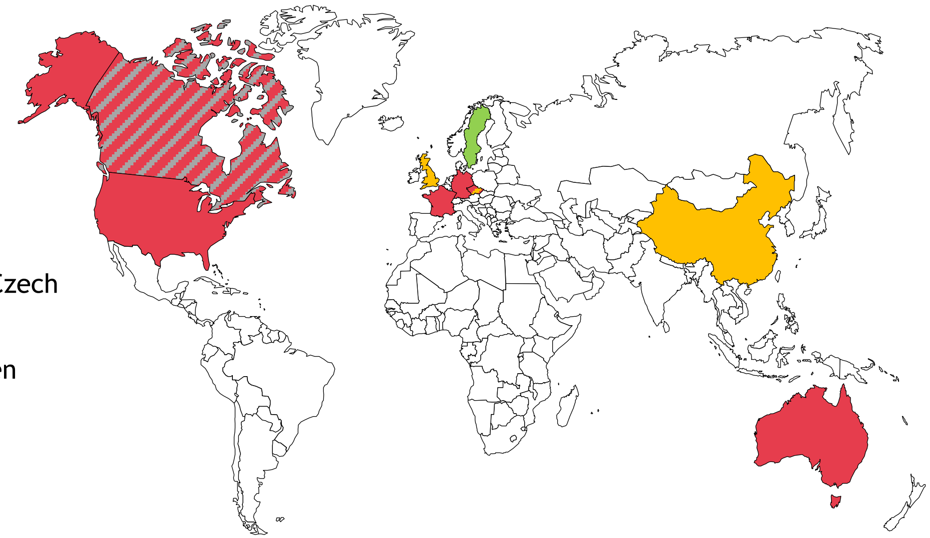
Epidemiological studies among miners :

Uranium
Canada (Ontario, Port Radium, Beaverlodge)
United States (Colorado, Nouveau Mexico)
Czech Republic, France, Germany, Australia

Fluorspar - Canada (Newfoundland)

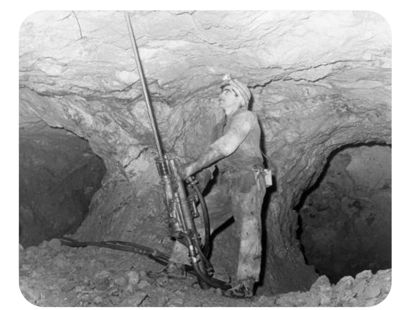
Tin
China, UK, Czech Republic

Iron - Sweden



Miners: relevant population

- Chronic exposure to Ionizing Radiations (IR), especially to radon
- Exposure to low / relatively high doses (according to cohort/period)
- Good quality of follow-up: mortality, administrative, dosimetric data



Contribution in public health and radioprotection

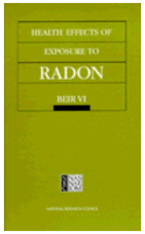
- Refine knowledges on health risks due to IR for low doses exposure (to provide information allowing to describe risks associated with radon exposure)
- Contribute to improve norms of radioprotection
- Contribute to assess the risks associated with indoor radon

↗ Pooled analysis of 11 underground miner cohort studies (BEIR VI, 1999)

Place	Country	Type of mine	Follow-up period	N miners	Person-Years*	N lung cancer	Cumulative expo (WLM)	ERR / 100 WLM
Yunnan	China	Tin	1976-1987	13,649	134,842	936	286.0	0.17
W-Bohemia	Czech Rep	Uranium	1952-1990	4,320	102,650	701	196.8	0.67
Colorado	US	Uranium	1950-1990	3,347	79,556	334	578.6	0.44
Ontario	Canada	Uranium	1955-1986	21,346	300,608	285	31.0	0.82
Newfounland	Canada	Fluorspar	1950-1984	1,751	33,795	112	388.4	0.82
Malmberget	Sweden	Iron	1951-1991	1,294	32,452	79	80.6	1.04
New Mexico	US	Uranium	1943-1985	3,457	46 800	68	110.9	1.58
Beaverlodge	Canada	Uranium	1950-1980	6,895	67,080	56	21.2	2.33
Port Radium	Canada	Uranium	1950-1980	1,420	31,454	39	243.0	0.24
Radium Hill	Australia	Uranium	1948-1987	1,457	24,138	31	7.6	2.75
CEA-COGEMA	France	Uranium	1948-1986	1,769	39,172	45	59.4	0.51
TOTAL				**60,606**	**888,906**	**2,674**	**164.4**	**0.59**

* Among exposed. WLM: Working Level Month. ERR: Excess Relative Risk. SE: multiplicative Standard Error

- ↗ risk of lung cancer with cumulative radon exposure
- Modifying effect of age at exposure (↓) and time since exposure (↓)
- Sub-multiplicative interaction between radon and smoking
- No evidence of other health effect associated with radon exposure

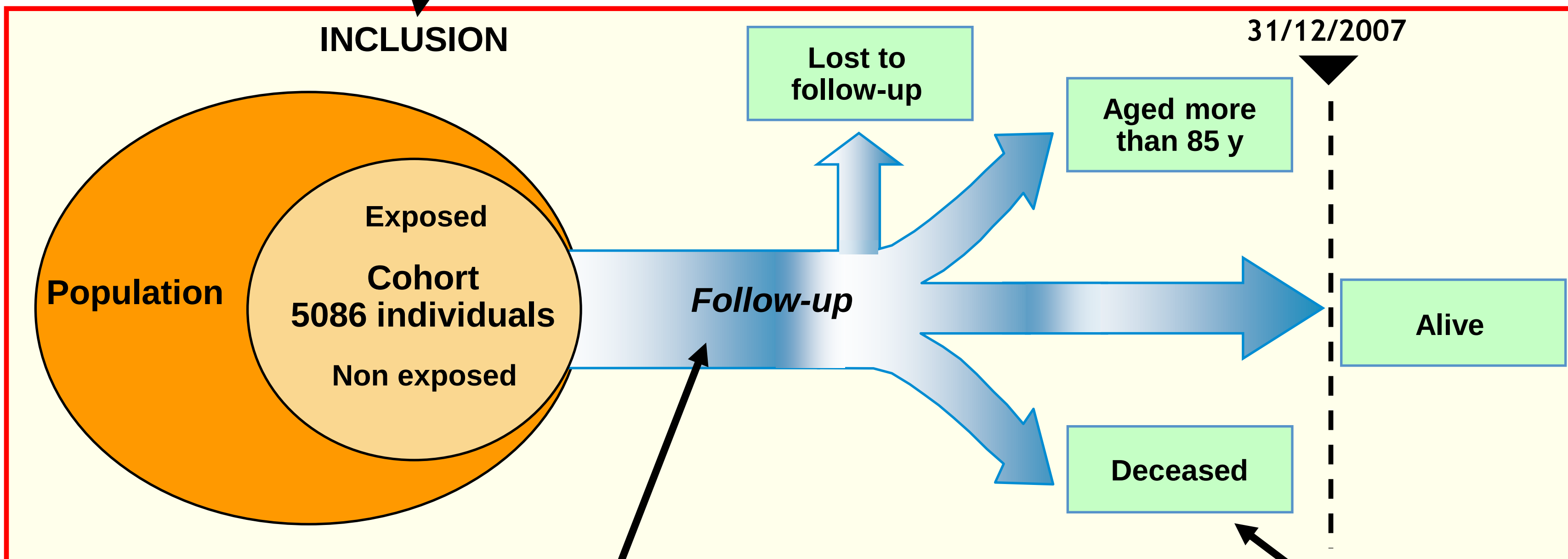


↗ The French cohort of uranium miners: Design of the study

- Miner employed by the CEA-COGEMA company (AREVA since 2006)
- Male
- Employed for at least one year between 1946 and 1990
(AREVA administrative database)

Vital status

from National database (RNIPP)



Occupational history

(AREVA administrative database)

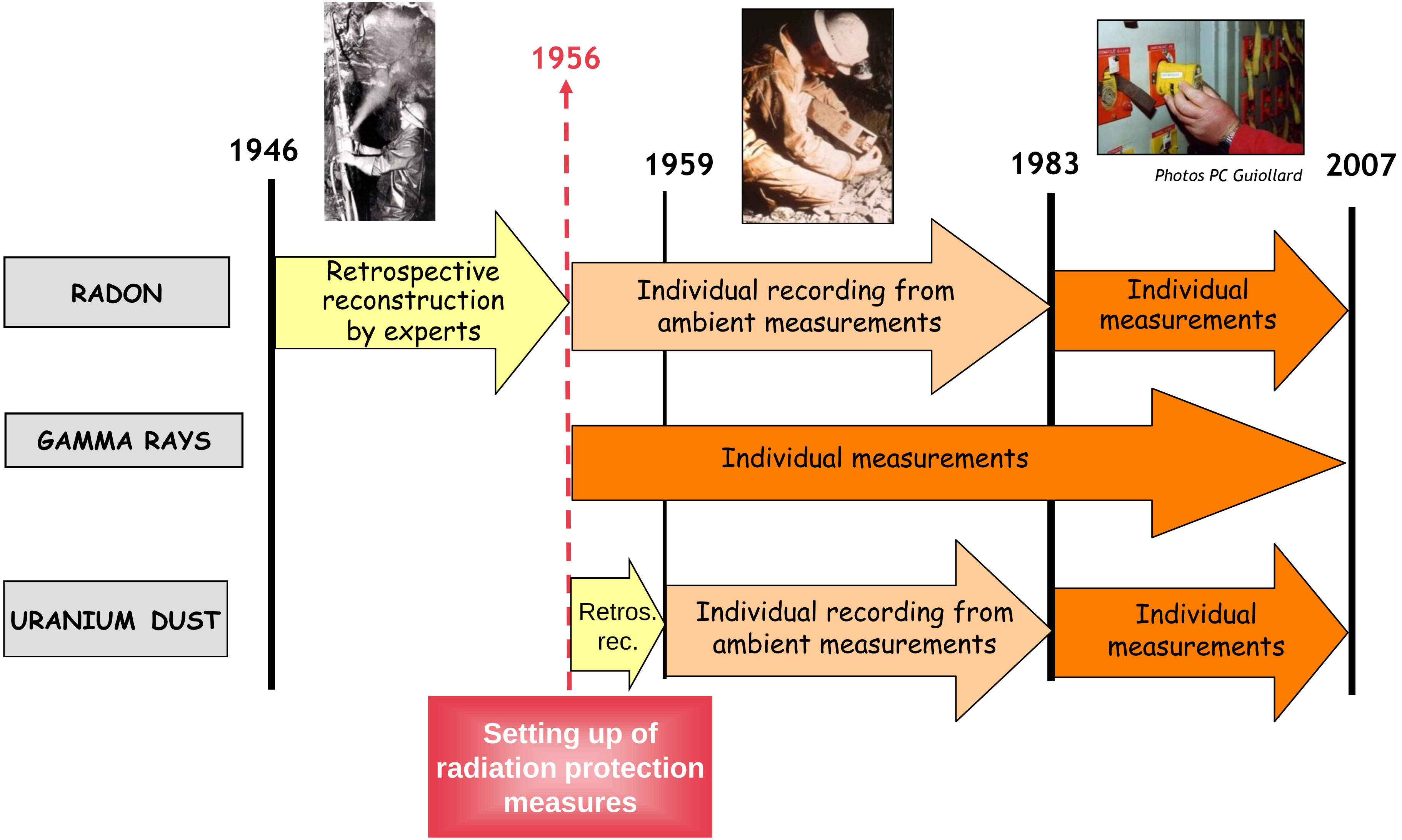
Annual occupational exposures

(AREVA, ALGADE)

Causes of death

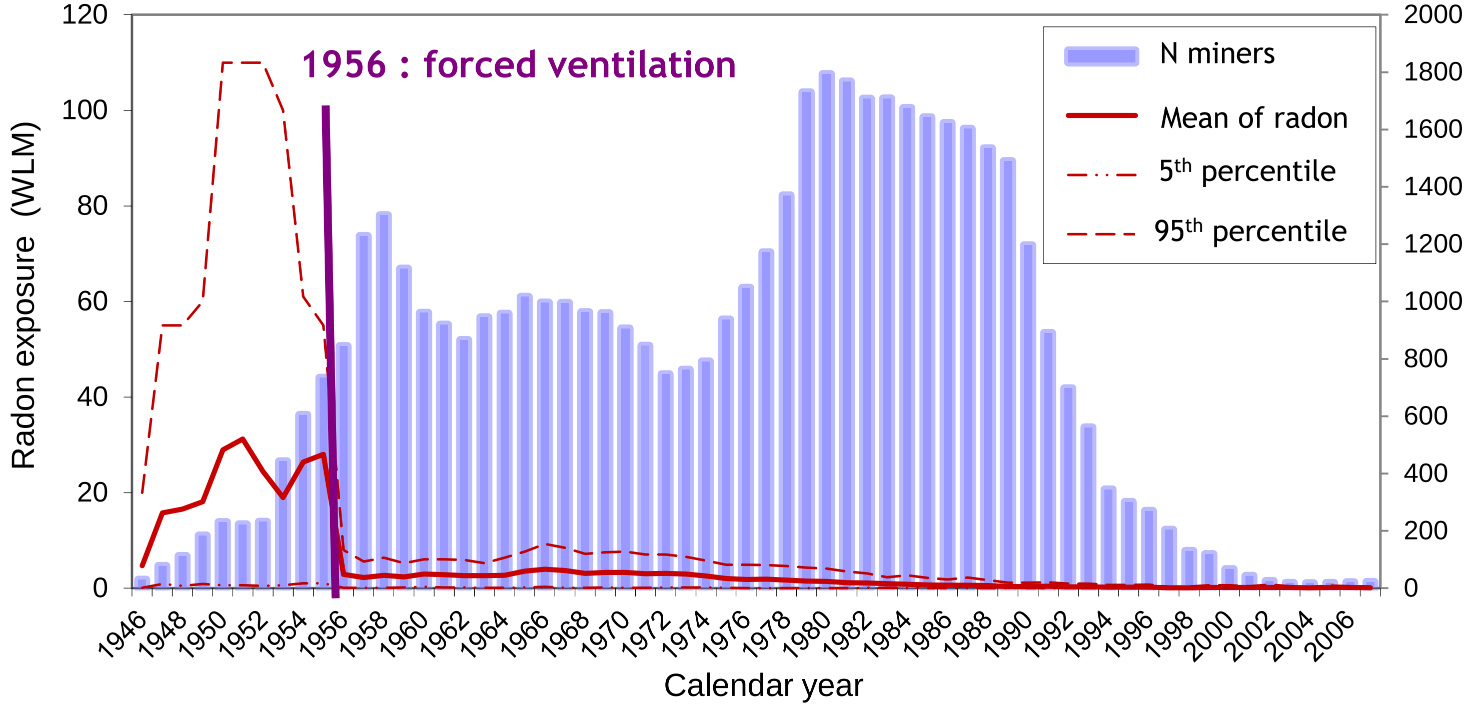
from National database (CépiDC)
And Occupational medical service of AREVA (complementary)

↗ French cohort: Assessment of IR exposures



French cohort: Assessment of IR exposures

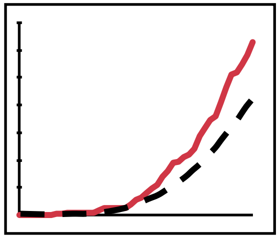
- Distribution of the number of exposed miners and of Radon exposure per year



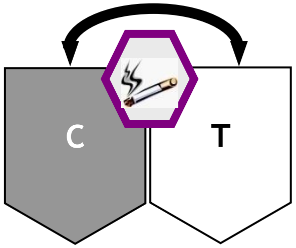
Radon exposure	Mean (min-max)
Annual exposure < 1956 (WLM)	21.3 (0.1 – 99.0)
Annual exposure ≥ 1956 (WLM)	1.7 (0.1 – 15.3)
Cumulative exposure (WLM)	36.6 (0.1 – 960.1)
Duration of exposure (year)	11.8 (1.0 – 37.0)

↗ Radon exposure and lung cancer risk:

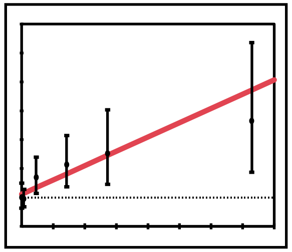
▌Main results among uranium miner studies



Excess of mortality
from lung cancer



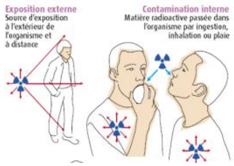
Smoking habits
Persistence of taking into account smoking habits



Radon exposure - lung cancer risk relationship

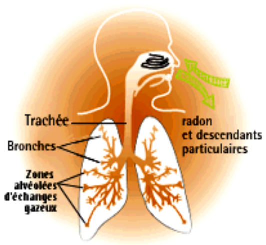
Persistence among miners with low exposure

Persistence after taking into account for measurement errors



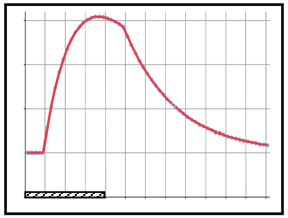
Multi IR Exposure

Persistence of the risk associated with radon exposure after taking into account for other IR exposure



Organ doses

Main contribution of radon to the lung dose



Modifying factors
Decrease of the risk with the time since exposure

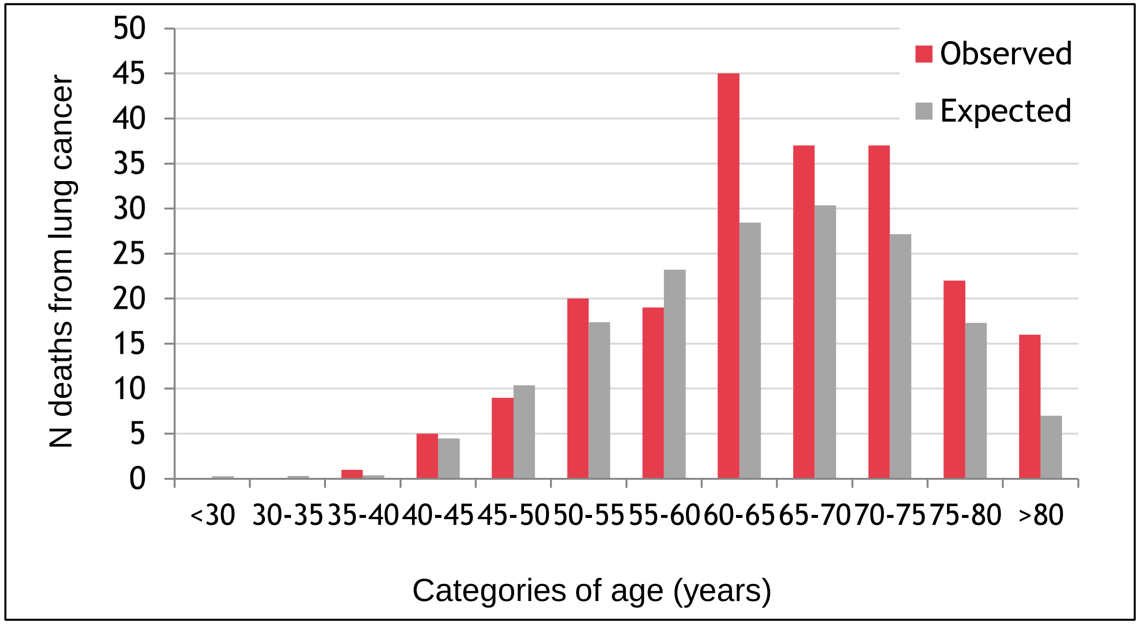
Mortality Analyses

Standardized Mortality Ratio (SMR)

→ To assess mortality risks in the cohort in comparison to a reference (general population)

$$SMR = \frac{\text{number of observed deaths for the cohort}}{\text{number of expected deaths for the cohort}}$$

- Example of the French cohort



- Whole cohort

N=5,086; follow-up 1946-2007

N cases=211

Significant ↗ of mortality from lung cancer

SMR = 1.34 [95% CI:1.16-1.53]

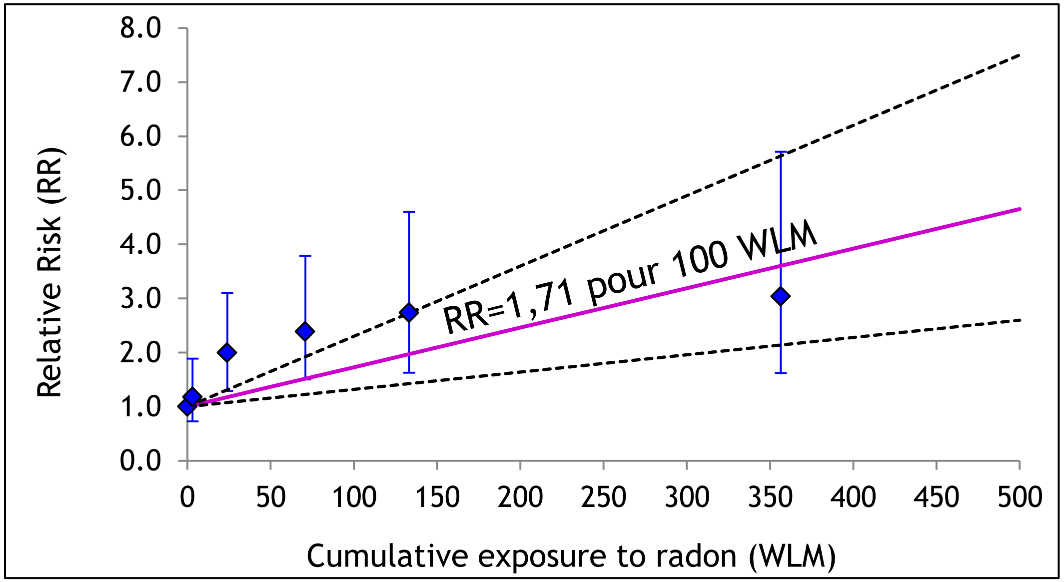
↗ Relationship between Radon exposure - Lung cancer Risk

Risk assessment: Excess Relative Risk (ERR) – Linear model

RR (t,w) = 1 + β w(t)

- RR(t,w) : Relative Risk of death from lung cancer for a cumulative expo to radon w at a t moment compared to the baseline risk
- β: Excess of Relative Risk (ERR)
- w(t) : Cumulative exposure at t time
- Poisson Regression
- 5-years lag

❑ Example of the French cohort



- Whole cohort
  N=5,086; follow-up 1946-2007
  N cases=211
- ERR for lung cancer death:
  ERR/100 WLM =
  0.71 [95%CI: 0.31-1.30%]
- Interpretation
  ↗ 71 % in the RR lung cancer death

[Rage et al, Int Arch Occup Environ Health 2015]

↗ Radon exposure - Lung cancer Risk relationship

Low level of radon exposure

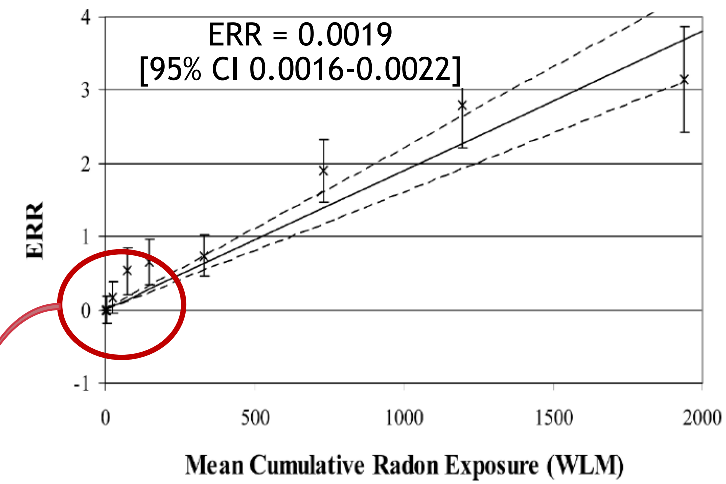
- Example of the French cohort
  - + 1955 cohort
    N=3,377; N cases=94 ; follow-up 1956-2007;
  - ERR/100 WLM = 2.42 [0.09-5.14]

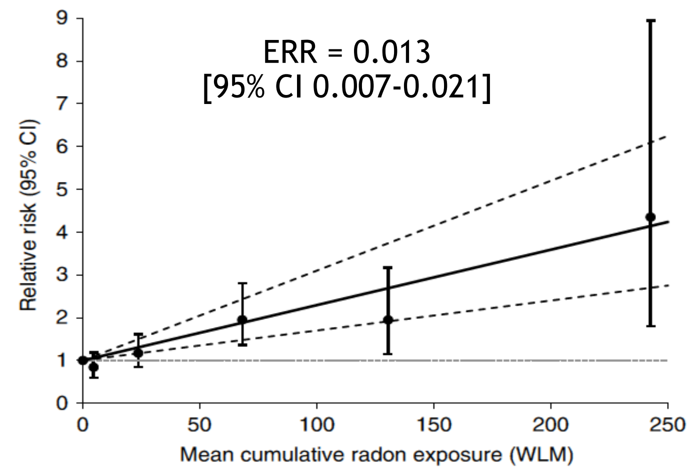
  [Rage et al, Int Arch Occup Environ Health 2015]

- Example of the German Wismut cohort
  - Whole cohort N=58,987; N cases = 3,016
    follow-up 1946-2003;

    [Walsh et al, Radiat Res 2010]
  - + 1960 sub-cohort N=26,766; N cases = 334
    follow-up 1960-2008;

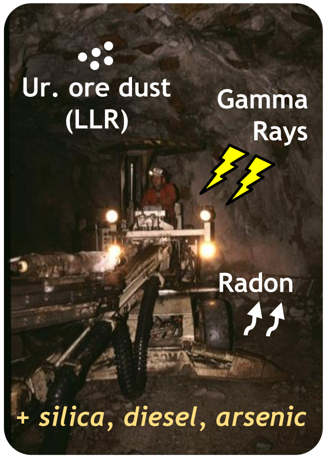
    [Kreuzer et al, Br J Cancer 2015]





⇨ Excess Relative Risk for lung cancer remained significant at low exposures

Multiple exposure to ionizing radiation (1)



IR exposure in uranium mines:

- Radon, external gamma ray, long-lived radionuclides (LLR)
- Some of uranium miner cohorts have assessed radon and other IR exposures

Relationship between Radon exposure – Lung cancer risk

- French +1955 sub-cohort (N = 3377 miners / N = 94 cases of lung cancer)

Causes of death	Type of exposure	ERR (%)	95% CI
	Radon (WLM)	2.42	(0.90 – 5.14)
Lung cancer	Gamma (mGy)	0.74	(0.23 – 1.73)
	LLR ($Bq.m^{-3}$ h)	0.032	(0.009 – 0.073)

→ Significant ERR associated with radon, but also to LLR and gamma separately

→ **But models** including all exposures together **could not be fitted**

- **Limitation due to:**

  - **high collinearity** between exposures (correlation coefficients r > 0.70)
  - size of the cohort and a **lack of statistical power**

[Rage et al, Int Arch Occup Environ Health 2015]

↗ Multiple exposure to ionizing radiation (2)

Relationship between Radon exposure – Lung cancer risk

- German +1960 sub-cohort (N = 26,766 miners / N = 334 cases of lung cancer)

	ERR /WLM)	95% CI
Crude model	0.013	(0.007 – 0.021)
Separate adjustment for		
external gamma rays	0.011	(0.004 – 0.019)
LLR	0.014	(0.007 – 0.022)

→ **Sufficient statistical power** to adjust for other IR exposures

→ **Significant ERR associated with radon remains** after considering other IR exposures

[Kreuzer et al, Br J Cancer 2015]

Dosimetric approach (1)

European collaborative Alpha-Risk Project (2005-2009)

- Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures:
  - Epidemiological studies: French, Czech, German cohorts of U miners
  - Calculation of doses to target organs

Alpha Miner Software

- Dosimetric Model (Human Respiratory Tract Model – ICRP Publication 66)
- Parameters of the aerosol
- Definition of different categories of job, mechanisation, type of mines, …

  → Different scenarios of exposure and different levels of physical activity

  [*Marsh et al, Heath Phys 2010; Marsh et al, Radiat Prot Dosimetry 2011*]

Calculation of lung doses

⇨ Absorbed doses (in gray) for each miner and for each year

Dosimetric approach (2)

Distribution of the cumulative absorbed lung doses

	French cohort		Czech cohort		German cohort	
N miners	3,271		9,979		29,086	
Mean (min-max) (in mGy)						
Non Alpha	55.97	(0.01-472.36)	54.29	(0.66-338.42)	39.52	(0.00-709.90)
Alpha	77.92	(0-700.00)	373.54	(0.36-4550.44)	272.73	(0.01-7282.36)

→ In terms of dose contribution:

Contribution of:	French cohort	Czech cohort	German cohort
Alpha dose to the total lung dose	58 %	87%	87%

Dosimetric approach (3)

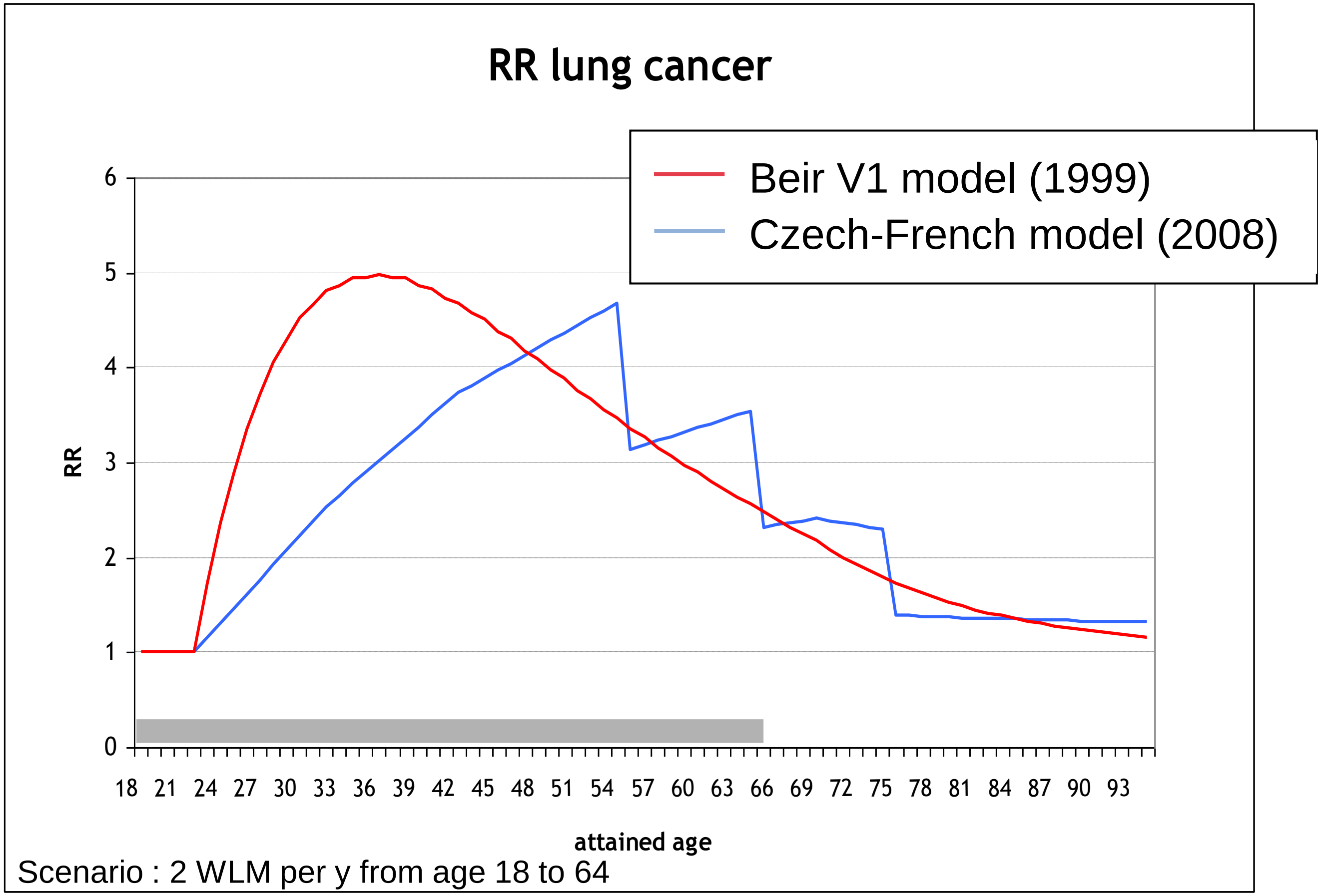
Relationship between Lung Doses – Lung cancer Risk

Alpha Risk Joint cohort (n = 1444 cases)	Separate regression		
	ERR / Sv	90% CI	p
Total dose	0.07	0.06 - 0.08	<0.001
Non alpha	15.70	12.60 - 19.40	<0.001
Rn gas + progeny	0.07	0.06 - 0.08	<0.001
LLR alpha	9.38	7.19 - 12.17	<0.001

- Significant association with **Total** and **Non-Alpha lung doses** in separate models
- Significant association with **Alpha component**, but large uncertainties on estimates for LLR
- In multivariate analyses, **ERR remained significant for Rn gas + progeny and LLR alpha**, whereas significant association with non alpha lung dose did not remain.

[Laurier D, et al. Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment. Alpha-Risk project deliverable D1.8. Analysis of risk among miners using organ dose calculation. Funded by the European Commission EC FP6 (Ref. FI6R-CT-2005-516483). European Commission DG XII, Brussels. (2009)]

↗ Modifying factors of the exposure-risk relationship



[Tomasek et al., Radiat Res 2008]

Decrease of lung cancer risk
- with Time since exposure
- with Age at exposure (attained age)

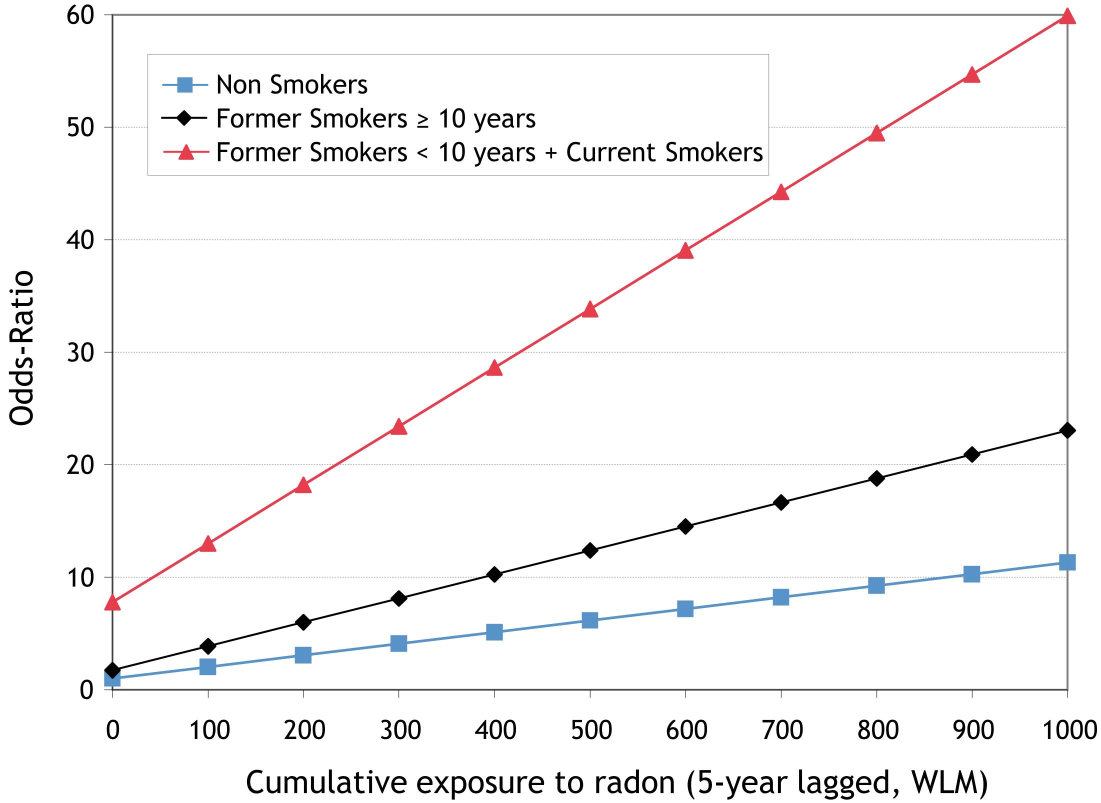
↗ Impact of Smoking habits

Joint European cohort

Nested case-control study

- France
- Germany
- Czech Republic

1,236 cases (lung cancer)
2 678 controls



- Significant Relationship between Radon exposure – Lung cancer risk remained after taking into account smoking habits
- The risk increased in each category of smoking
- Sub-multiplicative interaction

[Leuraud et al. Radiat Res 2011]

Epidemiological studies in the general population

↗ Indoor radon and lung cancer: case-control studies

Study	Year of publication	Country	Case/controls	RR per 100 Bq.m^{-3}	95% CI
Schoenberg	1990	USA (New Jersey)	480/442	1,49	0,89 - 1,89
Blot	1990	China	308/356	0,95	* - 1,08
Pershagen	1992	Sweden	201/378	1,16	0,89 - 1,92
Pershagen	1994	Sweden	1 281/2 576	1,10	1,01 - 1,22
Letourneau	1994	Canada	738/378	0,98	0,87 - 1,27
Alavanja	1994	USA (Missouri)	538/1 183	1,08	0,95 - 1,24
Auvinen	1996	Finland	517/517	1,11	0,94 - 1,31
Ruosteenoja	1996	Finland	164/331	1,80	0,90 - 3,50
Darby	1998	UK	982/3 185	1,08	097 - 1,20
Alavanja	1999	USA (Missouri)	247/299 372/471	0,85 1,63	0,73 - 1,00 1,07 - 2,93
Field	2000	USA (Iowa)	413/614	1,24	0,95 - 1,92
Kreienbrock	2001	Germany	1 449/2 297	0,97	0,82 - 1,14
Pisa	2001	Italy	138/291	1,40	0,30 - 6,66
Lagarde	2001	Sweden	436/1 649	1,10	0,96 - 1,38
Wang	2002	China	763/1 659	1,19	1,05 - 1,47
Lagarde	2002	Sweden	110/231	1,33	0,88 - 3,00
Kreuzer	2003	Germany	1 192/1 640	1,75 1,08	0,96 - 5,30 0,97 - 1,20
Baysson	2004	France	486/984	1,04	0,99 - 1,11
Bochicchio	2005	Italy	384/404	1,14	0,89 - 1,46
Wichmann	2005	Germany	2 963/4 232	1,10	0,98 - 1,30
Sandler	2006	USA (Connecticut, Utah)	1 474/1 811	1,002	0,79 - 1,21
Wilcox	2008	USA (New Jersey)	561/740	1,05	0,86 - 1,56
Turner	2011	USA	3 493/811 961	1,15	1,01 - 1,31
Brauner	2012	Danemark	589/52 692	1,04	0,69 - 1,56

↗ European case-control study (1/3)

Three joint studies

		Studies *n*	Cases *n*	Controls *n*	RR / 100 Bq.m^{-3} (95%CI)
European	*Darby 2005*	13	7 148	14 208	1.08 (1.03 - 1,16)
North American	*Krewski 2006*	7	3 662	4 966	1.10 (0.99 – 1.26)
Chinese	*Lubin 2004*	2	1 050	1 995	1.13 (1.01 – 1.36)

➡ Increase in the RR about 10 % per 100 Bq.m^{-3}

Joint European study in general population

- 13 studies in 9 countries: Belgium, Czech Republic, Finland, France, Germany, Great-Britain, Italia, Spain, Sweden
- Standardized protocol:
  - ✓ Identical inclusion criterias
  - ✓ Common questionnaire
  - ✓ Reconstruction of indoor exposure for 30 years
  - ✓ Inter-comparison of the methods of measure
  - ✓ Joint analysis of individual data
- Population: 7,148 cases / 14,208 controls

↗ European case-control study (2/3)

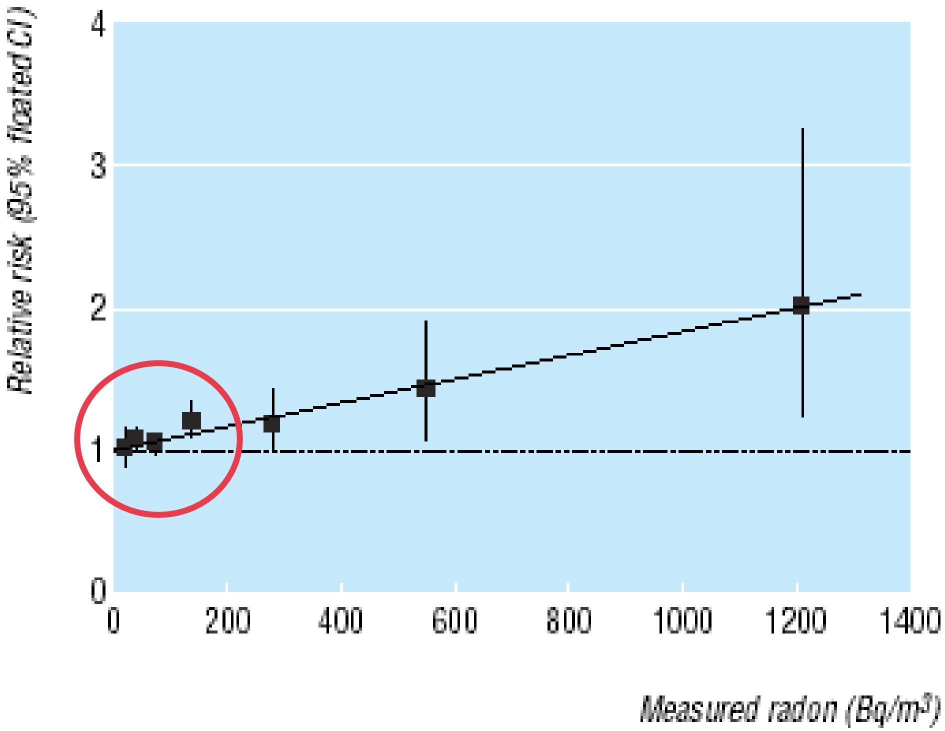
- Indoor mean radon concentration

  Cases = 104 Bq.m^{-3}
  Controls = 97 Bq.m^{-3}

- ↗ risk of lung cancer
  with radon concentration

RR = 1.08 per 100 Bq.m^{-3} [1.03 – 1.16]

RR = 1.16 per 100 Bq.m^{-3} [1.05 – 1.31]
after consideration of uncertainties related to estimations of radon concentration

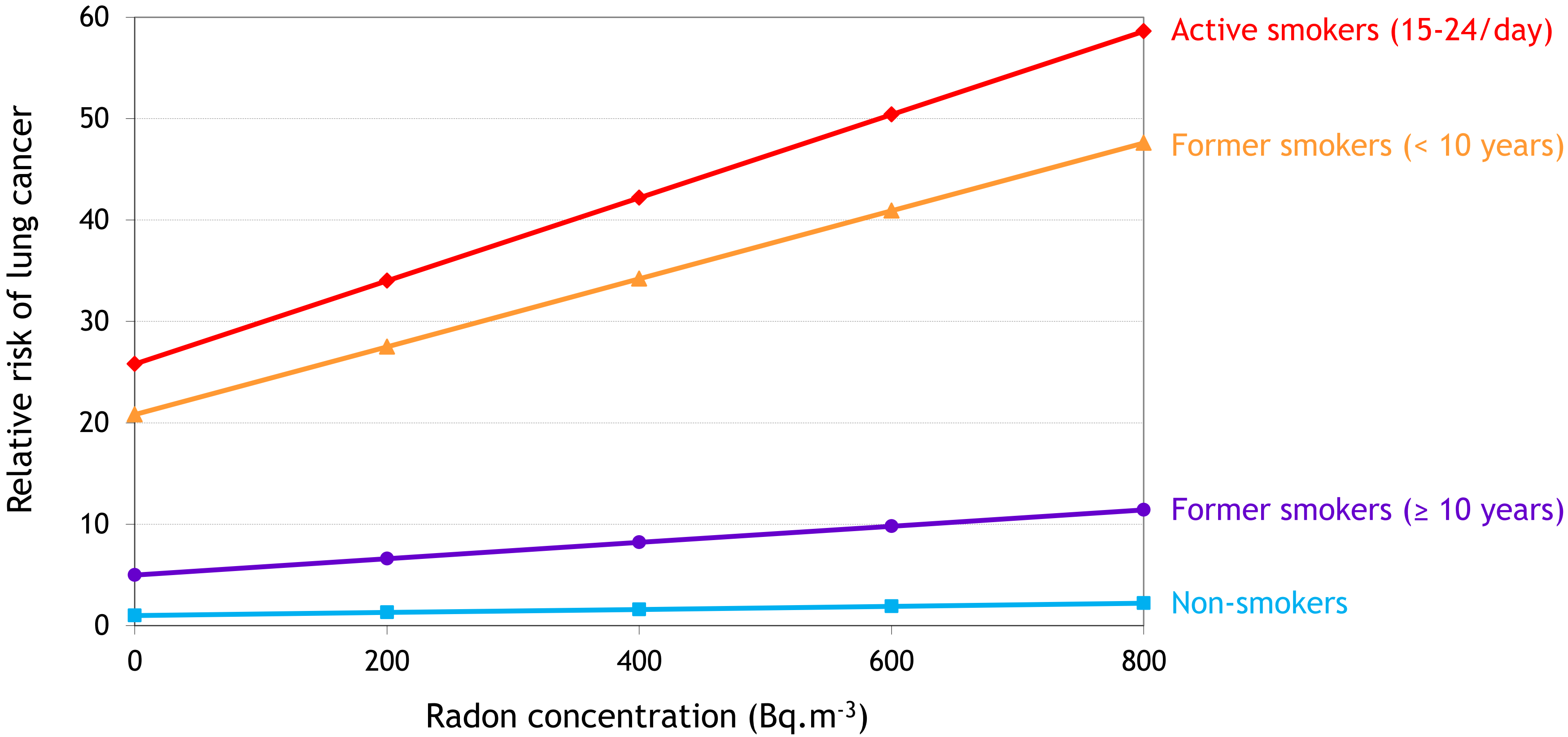


- Significant relationship for exposures < 200 Bq.m^{-3}

[Darby et al. BMJ 2005]

↗ European case-control study (3/3)

- Joint effet of radon and smoking



➡ Significant relationship with radon among smokers and non-smokers

[Darby et al. Scand J Work Environ Health 2006]

↗ Population attributable fraction of lung cancer mortality from residential radon

[Gaskin et al. Environ Health Physics 2018]

Countries	Radon exposure ($Bq.m^{-3}$)	Attributable fraction for lung cancer from residential radon (%)				
		BEIR VI [a]	Hunter [b]	Kreuzer [c]	Krewski [d]	Darby [e]
Cuba	5	4,3	2,3	2,1	1,6	1,2
Australia	9	4,7	3,7	3,5	2,1	1,6
United Kingdom	14	8,0	5,8	5,4	4,1	3,1
Algeria	22	15,8	9,0	8,3	6,4	4,8
China	34	15,9	13,1	12,4	9,5	7,2
Canada	42	16,3	15,5	14,6	11,2	8,6
France	50	19,4	17,8	16,9	13,0	10,0
Sweden	67	19,2	22,4	21,2	16,3	13,0
Mexico	82	26,7	25,9	24,9	19,3	15,4
Czech Republic	94	24,3	28,9	27,5	21,4	17,3
Poland	133	28,4	36,1	34,8	27,3	22,6
66 countries (median)	38	16,5	14,4	13,6	10,4	8,4

Radon exposure: national geometric mean (in 2012)

[a] EAC Model « exposure age concentration », joint analysis 11 miner cohorts, BEIR VI (NRC 1999)

[b] Three European joint analysis on miners (Hunter et al. 2013)

[c] German cohort of uranium miners (Kreuzer et al. 2015)

[d] North-American joint analysis in the general population (Krewski et al. 2003)

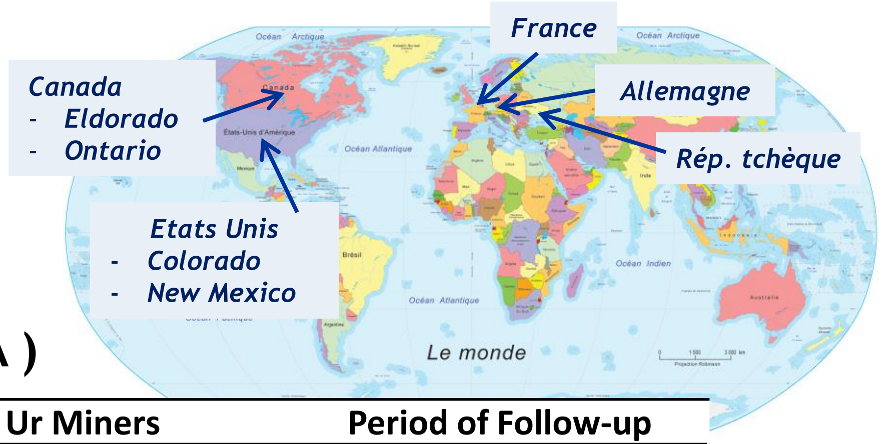
[e] European joint study in the general population (Darby et al. 2006)

➡ Consistence in findings according to the models (based on miners studies)

↗ Summary of knowledges on lung cancer risk and radon exposure

- Good **consistence among results** from studies among miners and in the general population
- Persistence of lung cancer risk **at low level of radon**
- Increased risk observed among smokers as well as **non smokers**
- **Smoking-radon interaction** between additive and multiplicative effect
- **Lung cancer**: to date, the only highlighted risk associated with radon *(studies on leukemia, skin cancer, brain cancer, stomach cancer, …)*
- Lack of knowledge on the effect of radon exposure during childhood

↗ Perspectives



International joint cohort

- **Pooled Uranium Miners Analysis (PUMA)**

Country, Place	Ur Miners	Period of Follow-up
Canada, Ontario	28,546	1954-2007
Canada, Beaverlodge	9,498	1950-1999
Canada, Port Radium	3,047	1950-1999
Czech Republic	9,978	1952-2010
France	5,086	1946-2007
Germany	58,976	1946-2013
USA, Colorado Plateau	4,137	1960-2005
USA, New Mexico	3,469	1943-2012
Total: Pooled study	**126,733**	

Objectives

- Set up a large international cohort of uranium miners
- Increase the statistical power
- Improve the assessment of the relationship between radon exposure and:
  - Risk of Lung cancer risk (refinement, modifying factors, low exposure, …)
  - Risk of cancer other than lung
  - Risk of non cancer disease

Thank you