Cancer risk from radon exposure: recent results from uranium miners studies

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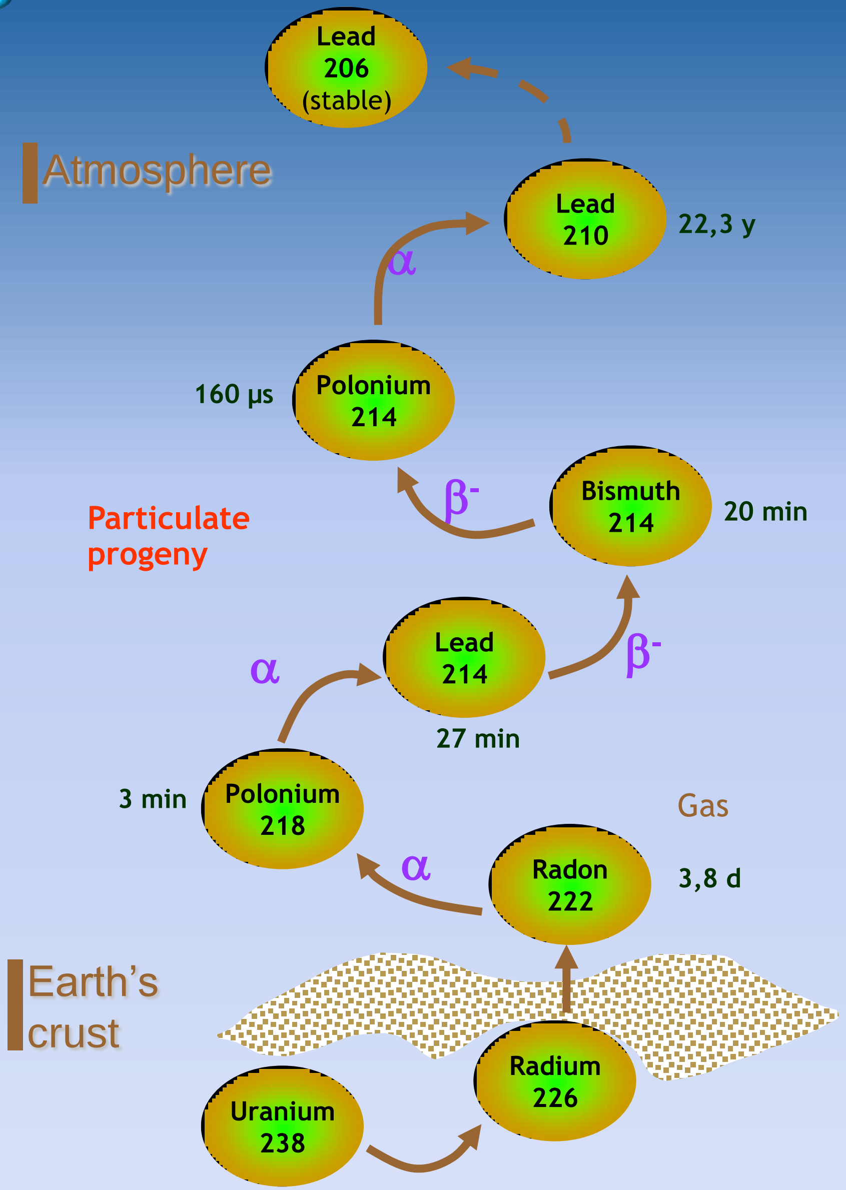
ICRP Committee 1

Radon and lung cancer risk

- Radioactive gas of natural origin, present everywhere, concentrates in confined places
- Emitter of α particles
- Inhalation leads to irradiation of the bronchial epithelium
- Classified as a pulmonary carcinogen by the International Agency for Research on Cancer in 1988
- Quantification of the exposure-risk relationship at relatively low annual doses :
    - Answer from miners and indoor epidemiological studies
    - Interaction with tobacco



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The Alpha-Risk European Research Project

Alpha-Risk
FP6 Project no. 516483 (2005-2009)
www.alpha-risk.org

Uranium Miners

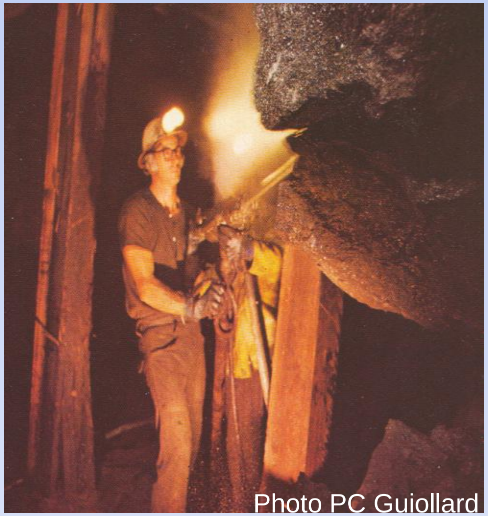


Photo PC Guiollard

- **Three European cohorts of uranium (U) miners**
  - **France, Czech Republic, Germany**
- **Individual smoking information**
  - **not available for the whole cohorts**
  - **studied under a nested lung cancer case-control approach**

Miners cohort studies

The Alpha-Risk Project
(EC FP6, 2005-09, Contract n° 516483
Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures

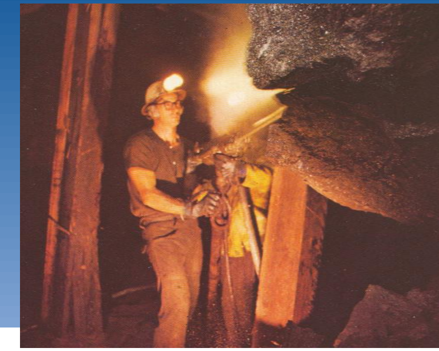
http://www.alpha-risk.org

	France	Czech Republic	Germany	Total
Population size	5,086	9,979	35,084	50,149
Follow-up period	1946 – 1999	1952-1999	1955-1998	1946 – 1999
Person-years	153,047	262,507	908,661	1,324,215
Duration of follow-up (y)	30.1	26.3	25.9	26.4
Number of death	1,467	3,947	4,519	9,933
Lung cancer	159	922	462	1 543
Radon				
Cumulative exposure (WLM)	36.6	72.8	55.9	58.0
Duration of exposure (y)	11.7	6.9	8.9	8.8

***Working Level Months** (WLM): unit of radon exposure. any combination of radon progeny in 1l of air which results in the emission of 130,000 MeV of energy from alpha particles x a monthly working time of 170 hours)*

(Tirmarche et al., Alpha-Risk 2010)

Exposure-risk relationship at low levels of exposure



Cohort	Whole cohorts		Low exposure rate period *	
	ERR/ 100 WLM	95%CI	ERR/ 100 WLM	95%CI
Czech	1.13	0.74–1.53	2.14	1.21–3.08
French	0.60	0.17–1.03	2.11	0.78–3.44
German	0.41	0.27–0.55	3.76	2.13–5.39
Joint	-		2.60	1.83–3.36

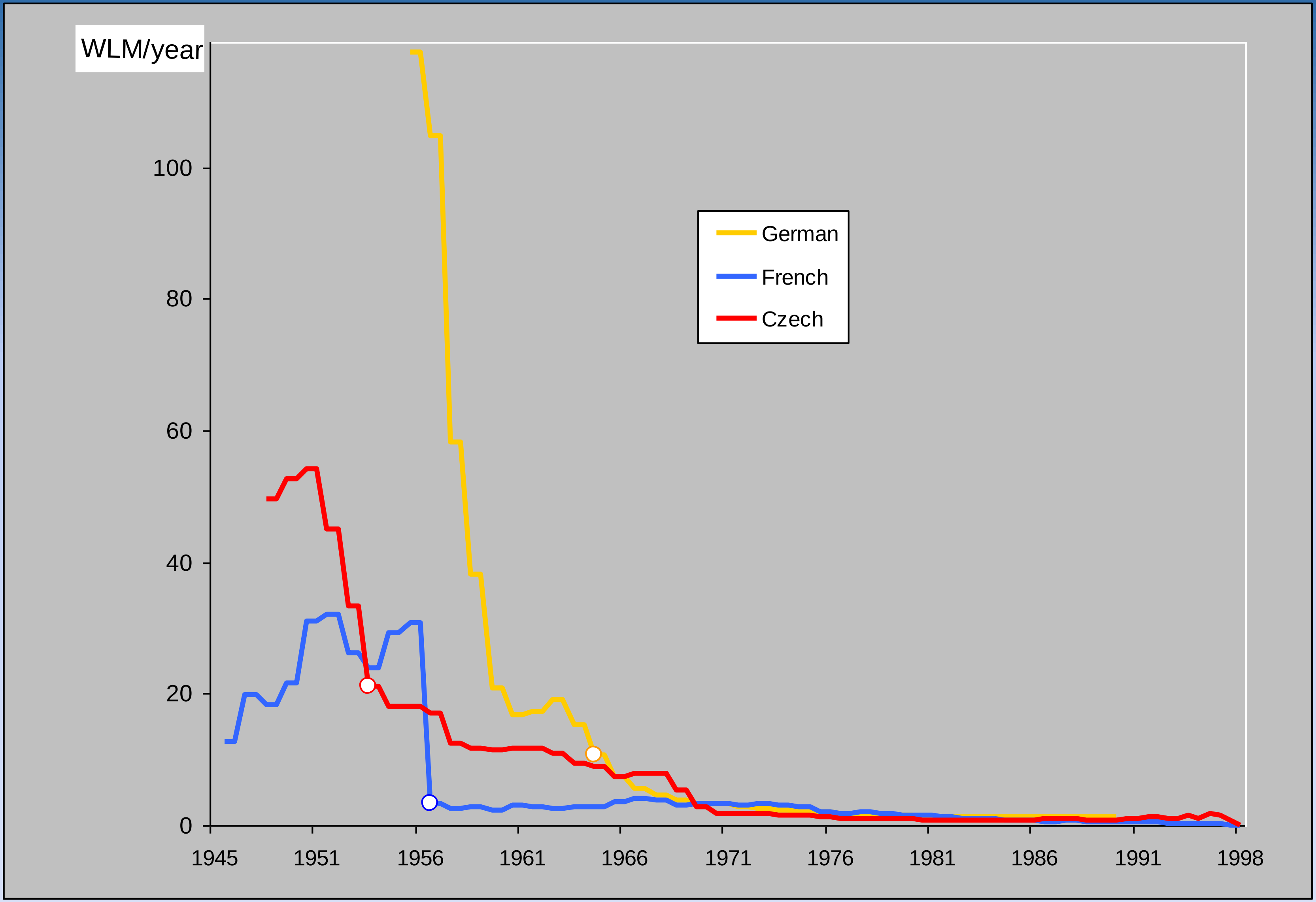
models stratified on the birth year and the country

* exposures since 1953, 1956 and 1967, respectively in the Czech, French and German cohort

(Tirmarche et al., Alpha-Risk 2010)

Higher risk coefficients at low levels of exposure
Good coherence between estimates from the 3 cohorts

Mean Annual Exposures in the Studies



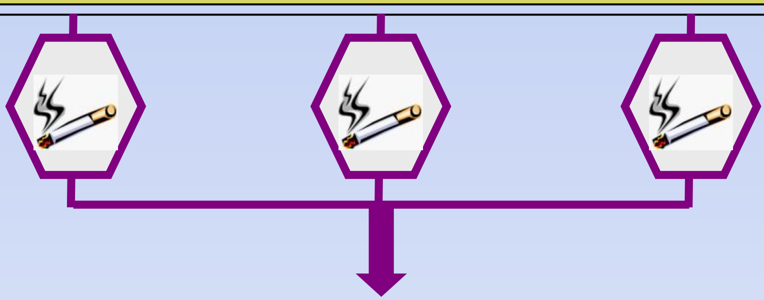
cut points correspond to largest difference in period specific estimates of ERR/WLM

Pooled nested case control study

	France	Czech Rep.	Germany	Total
Cases / controls	100 / 500	672 / 1491	704 / 1398	1476 / 3389
Cases / controls with smoking information	60 / 310	672 / 1491	314 / 691	1046 / 2492
	Leuraud et al, Health Phys 2007	Tomasek, Rad Prot Dosim 2011	Schnelzer et al, Health Phys 2010	

European cohort of uranium miners

	France	Czech Republic	Germany	Combined Cohort
Population	5086	9979	35084	50149
Follow-up period	1946 – 1999	1952-1999	1955-1998	1946 – 1999
Person-years	153 047	262 507	908 661	1324 215
Follow-up duration	30.1	26.3	25.9	26.4
Attained age (y)	58.9	56.6	48.6	51.2
Number of deaths	1467	3947	4519	9933



Nested case-control study

Lung cancer risk associated to radon exposure and smoking

Cumulative radon exposure (5-year lagged, WLM)	Never smoker	Ex-smoker ≥ 10 y	Ex-smoker < 10 y + current smoker
< 50	**1**	**1.9 (0.8-4.3)**	**7.2 (3.6-14.6)**
50-100	**2.1 (0.8-5.2)**	**3.9 (1.6-9.8)**	**12.0 (5.7-25.2)**
100-200	**2.0 (0.8-5.0)**	**5.0 (2.1-11.6)**	**18.6 (9.0-38.6)**
200-400	**4.9 (1.9-12.5)**	**6.3 (2.6-15.2)**	**21.0 (10.0-44.1)**
≥ 400	**7.1 (2.4-20.6)**	**16.8 (6.8-41.6)**	**36.7 (16.9-279.6)**

WLM: Woking Level Month

Risk increases with both smoking and cumulative radon exposure

Excess relative risk of lung cancer associated to radon exposure

	ERR per WLM (95%CI)
Unadjusted on smoking	0.010 (0.006-0.018)
Adjusted on smoking	0.008 (0.004-0.014)
Among never and long term ex-smokers	0.012 (0.005-0.026)
Among short term ex- and current smokers	0.007 (0.003-0.013)

Risk increases with cumulative radon exposure among smokers and non

(submultiplicative interaction, ref. Leuraud et al. Rad Research 09/2011,176,3)

Context for risk assessment

- Radon associated risk estimated by the ICRP in report 65 (1993)
- New results from epidemiological studies (miners and general population) since ICRP 65
- Evidence of a significant relationship between exposure to radon and radon decay products and lung cancer risk
- Evidence for modifying factors of the exposure-risk relationship from miners studies (age, time since exposure)

TASKGROUP64 of C1 summarizes available knowledge and proposes new calculation of lifelong risk

What is the impact of new results compared to the ICRP 65 ?

Are results from miner studies and indoor studies coherent ?

What is the coherence with recent position of Unscear and WHO

ICRP 65 : radon lifetime risk

(ICRP 65, 1993, Annex A)

Risk coefficient

7 miners mortality studies

Projection model

multiplicative model

modifying effect of age at exposure and time since exposure

Lifetime

cumulated risk up to age 90

Background rates

mixed population (ICRP 60) : both sexes, 5 countries

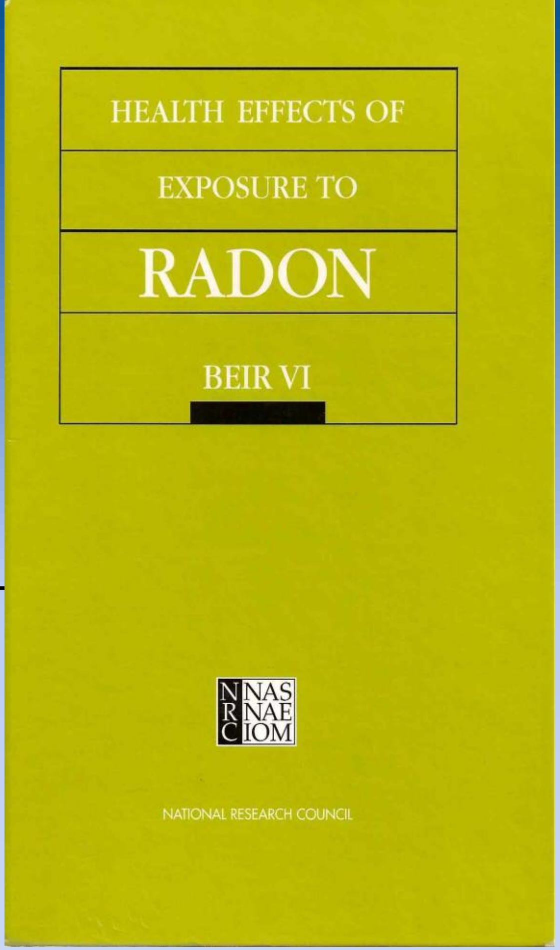
Exposure scenario

chronic exposure to 2 WLM from age 18 to 64

→ **Lifetime Excess Absolute Risk : 2.8 10^{-4} per WLM**
(fatality coefficient)

Working Level Months *(WLM): unit of time-integrated radon exposure. any combination of radon progeny in one liter of air which results in the ultimate emission of 130,000 MeV of energy from alpha particles x a monthly working time of 170 hours)*

BEIR VI Risk model (NRC 1998)



11 cohorts

- > 60,000 miners
- > 2600 lung cancer deaths
- mean exposure 164 WLM (max > 10000 WL

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
- ERR/100 WLM below 50 WLM 1.18 [0.2 – 2.5]

Calculation of Lifetime Excess Absolute Risk (LEAR)

Lifetime risk calculation: LEAR (Thomas D et al. Health Phys 1992)
(also called REID, Risk of Exposure Induced Deaths)

Risk model
Derived from published combined analyses
Relative risk models with modifying effects

Lifetime
90 y old (No risk before age 18)

Background rates: ICRP 103 2007
Mean M/F-Asian/Euroamerican
average population: 2 sexes, Euro-American / Asian

Exposure scenario: ICRP 65 1993
2 WLM per y from age 18 to 64 (cumulated 94 WLM)

Czech-French joint model

(Tomasek et al. Rad Res 2008)

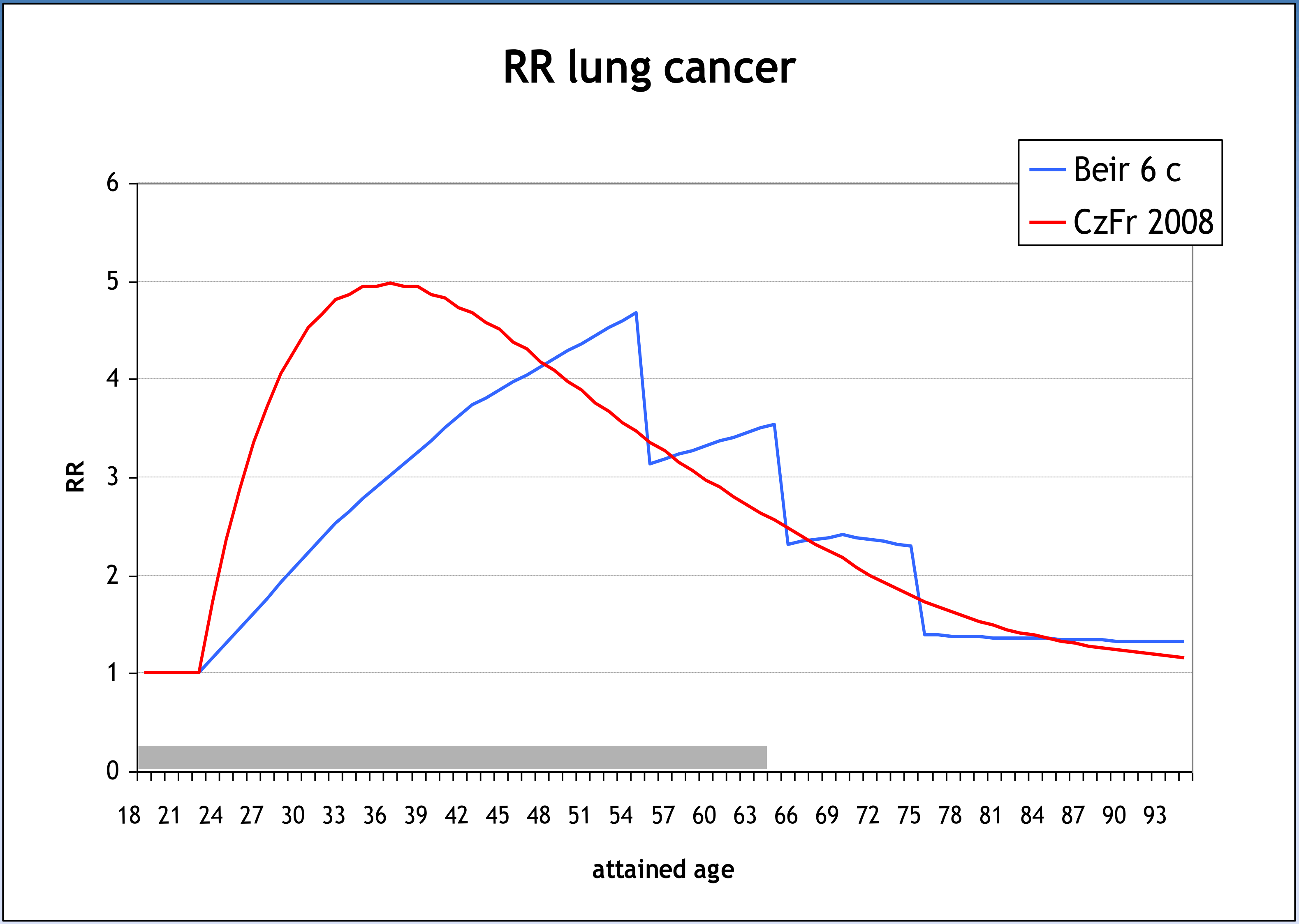
EC FP5 project
« Uminers + AI data »

Combined analysis of low exposed miners

Name-place	Country	Type of mine	Follow-up period	Nb miners	Nb lung cancer deaths	Cumul expo WLM	Person-years	ERR per 100 WLM
West Bohemia	Czech Republic	Uranium	1956-95	5002	449	57	133 521	
CEA-AREVA	France	Uranium	1946-94	5098	125	37	115 261	
Combined				10 100	574	47	248 782	1.6 [1.0 – 2.4]

- Agreement with a linear model
- ERR ↘ with Time Since Exposure
- ERR ↘ with Age at Exposure
- no inverse exposure rate effect

Variation of RR over time



Scenario : 2 WLM per y from age 18 to 64

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Lifetime Excess Absolute Risk (10^{-4} per WLM)

Mean Population (m+f/asian+euroamerican)		
	Beir 6 c	CzFr 2008
18-89	5.38	4.84

➡ **To be compared to the ICRP 65 value of 2.8 10^{-4} per WLM**

Scenario 1 : 2 WLM per y from age 18 to 64

Lifetime Excess Absolute Risk (10^{-4} per WLM)

Mean Population (m+f/asian+euroamerican)

	Beir 6 c	CzFr 2008	Fr post56	Eldorado 2006	Wismut 2006
18-89	5.38	4.84	7.60	6.77	3.09

→ **Sensitivity to risk model**

Scenario 1 : 2 WLM per y from age 18 to 64

Lifetime Excess Absolute Risk (10^{-4} per WLM)

Mean Population (m+f/asian+euroamerican)

	Beir 6 c	CzFr 2008
18-69	3.69	3.25
18-89	5.38	4.84
18-94	5.41	4.85

➡ **Sensitivity to lifetime duration**

Scenario 1 : 2 WLM per y from age 18 to 64

Lifetime Excess Absolute Risk (10^{-4} per WLM)

Mean Population (m+f/asian+euroamerican)

	Beir 6 c	CzFr 2008
18-89	5.38	4.84

Male Euroamerican Population

	Beir 6 c	CzFr 2008
18-89	7.18	6.40

Sensitivity to background rates

Scenario 1 : 2 WLM per y from age 18 to 64

Pooled residential studies

Indoor data – primary risk coefficients

Joint analysis	Number of studies included	Cases	Controls	Relative risk per 100 Bq m^{-3}	95% CI
Chinese *(Lubin et al., Int J Cancer 2004)*	2	1050	1995	1.13	(1.01-1.36)
European (Darby et al., BMJ 2005)	13	7148	14208	1.08	(1.03-1.16)
North American *(Krewski et al., Epidemiol 2006)*	7	3662	4966	1.10	(0,99-1.26)

➡ **Very good coherence of results from different indoor studies**

Comparison miner studies – indoor studies

Domestic radon- case control studies : European pooling

No modifying effect of attained age, age at exposure or time since exposure

Age at diagnosis: approx 70 y old

25 years of exposure reconstruction: 5 to 30 y before diagnosis (approx age 40 to 64)

Miner studies

Modifying effect of age at exposure and time since exposure

Men

Comparison of LEAR: if miners conditions similar to case-control studies

Lifetime age 70

Exposure scenario: 0.43 WLM (100 Bq/m^3) per y from age 40 to 64 (11 WLM)

Indoor primary coefficient for men

(Assuming 1 WLM == 1 year at 230 Bq.m^{-3} indoor (ICRP 65, 1993))

Cumulated Excess Absolute Risk (10^{-4} per WLM) - comparison of miners and indoor models

Mean Population (m+f/asian+euroamerican)

	Beir 6 c	CzFr 2008	Darby 2005
18-59	1.64	1.30	0.73
18-69	3.53	2.72	2.71
18-89	5.58	4.68	7.58

Good agreement of estimated cumulated risk
High sensitivity to lifetime duration

Scenario: 0.43 WLM (100 Bq/m3) per y from age 40 to 64

Conclusion

ICRP considered Lifetime Excess Absolute Risk of 5 10^{-4} per WLM
(to be compared with **2.8** 10^{-4} per WLM estimated by ICRP 65)

For risk communication, explain sensitivity to background rates and risk model (ERR value, modifying factors of the ERR) + duration of lifetime

Good coherence between risk estimates from miners and indoor studies (under appropriate conditions)

ICRP recommendations in line with those from other international committees (WHO, UNSCEAR…)

ICRP-C1-TG64 members involved in this radon risk assessment :

- From IRSN (France) : Eric Blanchardon; Dominique Laurier; François Paquet; Margot Tirmarche
- From HPA (UK) : John Harrison; James Marsh

Future plans : risk assessment for other alpha emitters www.icrp.org

Period specific ERR/WLM (in two exposure windows)

$$RR = 1 + b_{before} W_{before} + b_{after} W_{after}$$

Study	Cut points	ERR/WLM before	90%CI	ERR/WLM after	90%CI
Czech	1953	0.0069	0.0041 – 0.0107	0.0210	0.0147 – 0.0305
French	1956	0.0016	-0.0009 – 0.0057	0.0219	0.0120 – 0.0358
German	1964	0.0027	0.0017 – 0.0038	0.0206	0.0142 – 0.0282
		p = 0.012		p = 0.985	
				0.0210	0.0167 – 0.0261
					CV=14%

Lower ERR/WLMs from more distant periods (before) reflect

- higher uncertainty of earlier exposures (less measurements)
- potential overestimation of exposures (measurements conducted at workplaces with higher concentrations)
- exposure rate (cell killing because of high doses)
- potential decrease with time since exposure

Perspectives

International collaboration will continue

Aim : pooling studies to better quantify risks at low exposure

- Residential exposure: World pooling project
- Miners: Euro-Canadian initiative

Correction for measurement errors

(*Tirmarche, Alpha-Risk 2010; Allodji 2010*)

Continuation of collaboration between internal dosimetrists and epidemiologists

- Analyses based on organ dose-risk relationships
    - may contribute to new exposure-dose conversion convention coefficients for ICRP
    - Close collaboration with members of ICRP comittee2 (biokinetics models)

Development of molecular epidemiology among miners studies

(*Zolzer, ERRS 2010; Kreuzer, BfS 2010*)

Launching of studies on exposures during childhood

- Studies on childhood leukaemia risk in the UK and France