



Health effects of internal alpha emitters, contribution of epidemiology

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Experience of ICRP C1 taskgroup64: cancer risk related to alpha emitters

- Review over last 10-15 years publications
- Based on epidemiological studies with a good quality of individual exposure
 - to radon decay products (U miners + domestic exposure studies)
 - to uranium (workers during nuclear fuel cycle)
 - to plutonium (workers of Mayak, Sellafield....)
 - Taking account of other concomittant exposures: external gamma exposure, uranium dust, chemicals
 - + different conditions of solubility, metabolism, target organ



ICRP C1 taskgroup64: membership defined through necessary expertise of both epidemiology and dosimetry

- Cancer risk related to alpha emitters should be studied by calculating energy deposition on target organ : lung, liver....in mGy per year or cumulated over life.....
- Is it possible to take in account separate effects of alpha emitters and external gamma exposure
- How should be interpreted interaction of both,
- How should be modelised their influence on final risk, if both exposures are concomittant or separated over time period (initiator, promoter....)
- Is dosimetry on organ level influenced by concomittant smoking
- Quality factor of 20 ?
- Approach of a detriment calculation, example : comparison of cancer risk (lung cancer risk) from alpha emitters compared to H and N lung cancer risk



Experience from radon

Individual annual exposure in WLM (ambient measured individual exposure of radon daughters in eq with radon gas multiplied by duration) this unit can be converted (under some conditions) in organ dose (part of Alpha risk project)

A large number of studies, with individual assessment of exposure to external gamma, internal radon decay products and to uranium long lived dust :

Modelisation of time dependancy (dose rate effect, time since exposure, age at exposure)

Separate analysis for smokers and non-smokers,

Synthesis under WHO, BEIR 6, and ICRP115 :

good agreement when comparing results from miners and from general population

Management of risk :for domestic exposure: through Bq /m³

for workers (in mSv,see C2 of ICRP)

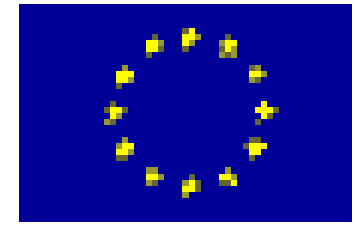
Comparison of lung cancer risk with results from H and N: ongoing research necessary



Radon

Major results





Czech-French (joint model)

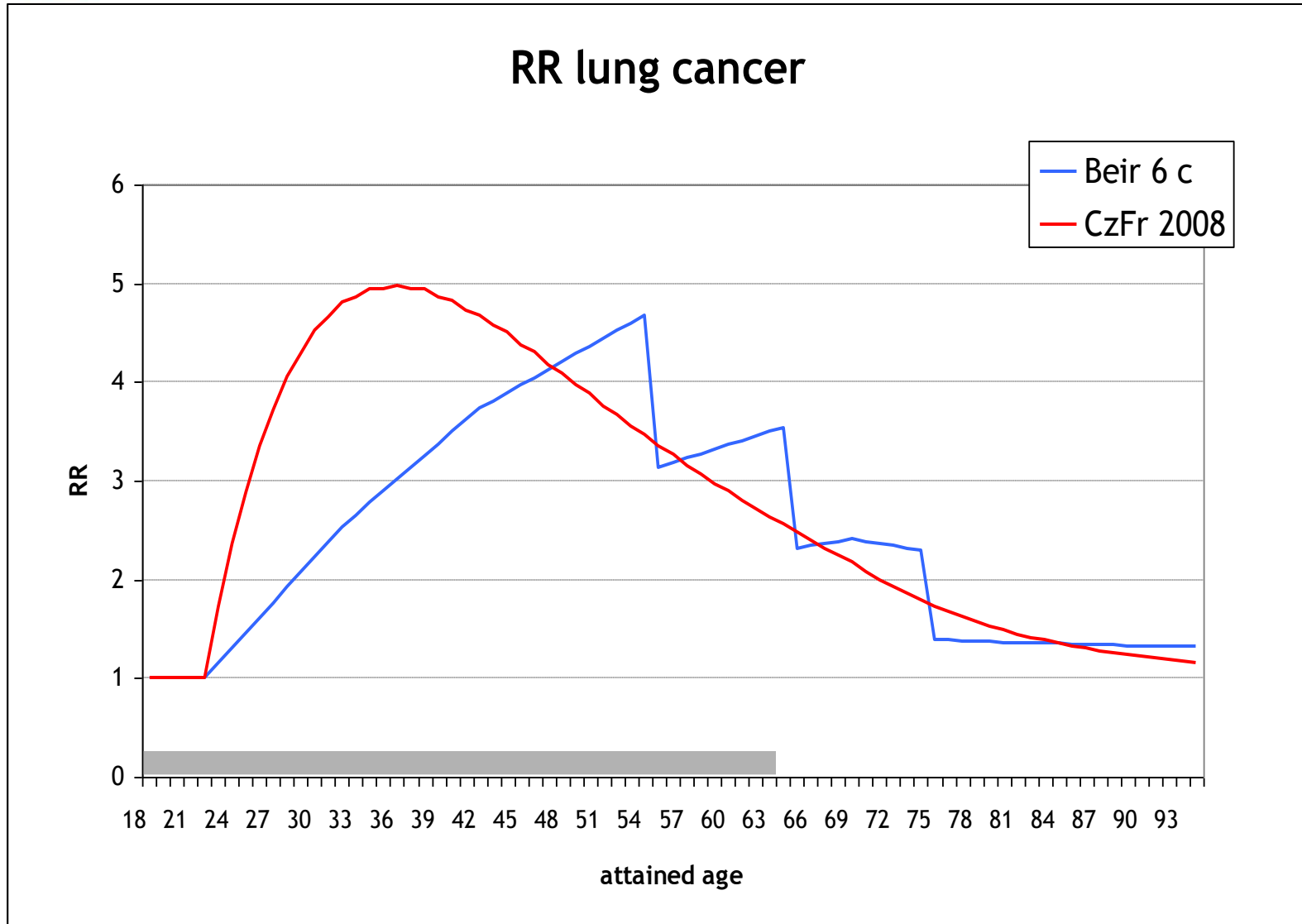
(Tomasek et al. Rad Res 2008)

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 \searrow with Time Since Exposure
- ERR \searrow with Age at Exposure
- no inverse exposure rate effect

Variation of RR over time

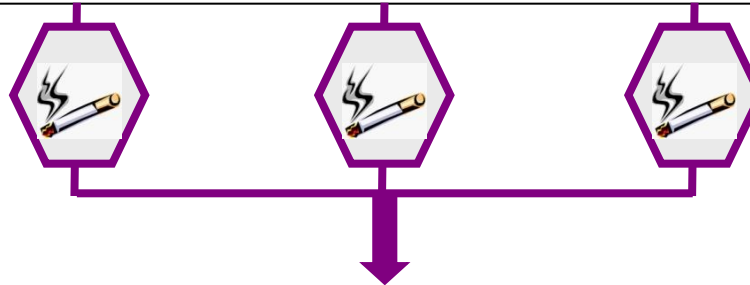


Scenario : 2 WLM per y from age 18 to 64



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





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

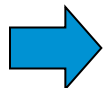
Tomasek,
Rad Prot Dosim
2011

Schnelzer et al,
Health Phys
2010



Lung cancer risk associated to radon exposure and smoking

Cumulative radon exposure (5-year lagged, WLM)	Never smoker	Ex-smoker \geq 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)
\geq 400 WLM: Working Level Month	7.1 (2.4-20.6)	16.8 (6.8-41.6)	36.7 (16.9-279.6)



Risk increases with both smoking and cumulative radon exposure (submultiplicative model)

Risk other than lung cancer ?

- Excesses observed among miners (leukaemia, kidney...)
 - need to extend follow-up + combined analyses
- Childhood leukaemia risk, linked to domestic exposure
 - some results with a positive trend (*Raschou, Evrard...*)
 - others don't show this positive relationship, ex Switzerland (Canupis) [Hauri et al, EHP 2013], UK (CCRG) [Kendall et al, Leukemia 2013]
 - Comment : natural background radiation = gamma + radon, bone marrow dose mainly influenced by external gamma exposure
 - Adjustment and co-factors is complicated (genetics, in utero exposure...)
- More research needed, as this is a possible childhood exposure, and should be focused on populations living in some specific “high background regions” : necessary collaboration with a joint analysis on international level (with precise calculation of organ doseincluding ingestion in early live)

Uranium

- In regard of the previously mentioned selection criteria, relatively few results available for a dose-response relationship linked to alpha emitters
- Indeed, most studies have only individual information of external dosimetry ,
 - some of them take in account internal exposure through a job matrix approach and all available information from bioassays (urine, or feces)
- During nuclear fuel cycle, different chemical forms of uranium, different solubility
- Missing values (frequency of bioassay, archives) influence total dose
- Target organ : lung, others.....

Uranium carcinogenicity in humans might depend on the physical and chemical nature of uranium and its isotopic composition: results from pilot epidemiological study of French nuclear workers

Guseva Canu et al (Cancer Causes Control 2011)

2097 workers from AREVA NC uranium processing plant (France) followed from 1960 to 2006.

- plant-specific job-exposure matrix : historical exposure history to different forms of uranium and chemicals
- Cox regression models stratified on sex and calendar period, and adjusted for socioeconomic status and potentially confounding co-exposures were used to estimate hazard ratios (HRs) for mortality from lung cancer (53 deaths) and lymphatic and hematopoietic tissue malignancies (21 deaths).
- **Results:** exposure to reprocessed uranium induce and increased risk of mortality from lung cancer and lymphatic and hematopoietic malignancies :the most significant HR being respectively 1.14 (95% CI: 1.00–1.31) and 1.20 (95% CI: 1.01–1.43) per unit of a time-lagged log-transformed continuous exposure scores
- HRs tend to increase with decreasing solubility of the compounds.
- Conclusion: Our results suggest that uranium carcinogenicity may depend on isotopic composition and solubility of uranium compounds. This study shows a possible carcinogenic effect of slowly soluble reprocessed uranium on two target organs. This finding is consistent with data from experimental studies.



Mortality and ionizing radiation exposures among workers employed at the Fernald Feed Materials Production Center

Silver et al., 2013 OEM

- NIOSH research project: risk of internal exposure to uranium
- Collaboration with industrial hygienists and dosimetrists (Anderson et al., 2012 IJEEH) (Anderson et al., 2012 Rad Prot Dosim)
- Cohort of uranium processing workers: sample size (n=6,409), and extended follow-up (more than 30 years of follow-up) (236568 PY)
- Internal doses to 5 target organs: lung, pancreas, large intestine, kidney, red bone marrow (automated calculation based on urinalysis data (+ uncertainties), **InDEP program**)
- Exposure to co-factors, chemicals, asbestos..(y/n) and gamma exposure (average 13,4 mGy) and radon (26 WLM)
- Mortality: lung cancer and chronic obstructive pulmonary diseases were in excess in those workers that were hourly hired, but the hazard's ratio for a continuous internal exp (at 0,1 mGy) was only of borderline significance for lung cancer . An ERR, excess rel risk of 1,5 per 0,1 mGy was observed for the lower large intestine
- Discussion : Internal dose to lung from Uranium was on average lower (1,1mGy) than from external gamma exposure (13,4mGy)
- Risk to large intestine ? Ingestion ?

Efforts for combining studies focusing on uranium exposed workers

- Under Alpha risk program : under WP4: a protocol for a cohort study was installed in France and in UK, in order to collect more data on an individual basis, history of exposure, bioassays, smoking data
- Aim : a large European computerized data basis with a common dosimetric approach and a future common epidemiological analysis
- In parallel, under WP3, a case control study on lung cancer and leukemia was planned for those nuclear workers, initially included in the IARC study, but with an internal exposure to Pu or Ur
- In the USA, same efforts are going on, focusing specifically on those workers with a good precision of individual internal exposure
- See also CURE project



Plutonium studies

- Mayak
- Sellafield

- Both under international collaborations (SOUL and SOLO + DOE support)





Recent publications of epidemiological studies of Mayak workers

Gilbert ES, et al Lung Cancer Risks from Plutonium: An Updated Analysis of Data from the Mayak Worker Cohort. *Radiation Research* 2013

- 14,621 Mayak workers who were hired in the period from 1948–1982, followed for at least 5 years, from 1953–2008: 486 deaths from lung cancer,
- Based on updated dose estimates (MWDS-2008)
- After adjustment for external radiation dose and smoking, the plutonium excess relative risk (ERR) per Gy declined with attained age and was higher for females than for males.
- ERR per Gy for males at age 60 was 7.4 (95% CI: 5.0–11)
- for females : 24 (95% CI: 11–56).
- Of the 486 lung cancer deaths, 105 (22%) were attributed to plutonium exposure and 29 (6%) to external exposure.
- from 12,708 workers with information on smoking: the relationship of plutonium exposure and smoking was likely sub-multiplicative

Labutina EV, et al. Radiation risk of malignant neoplasms in organs of main deposition for plutonium in the cohort of mayak workers with regard to histological types. Health Phys. 2013

- incidence study of malignant neoplasms in lung, liver, and bone and associated connective tissues among Mayak nuclear workers exposed to both internally incorporated plutonium and to external gamma radiation.
- 22,373 individuals employed at the reactors and radiochemical and plutonium production facilities of the Mayak nuclear complex during 1948-1982 and followed up to 2004
- A clear linear association between internal plutonium dose and the risk of lung cancer
- ERR)/Gy for adenocarcinoma was high (ERR/Gy = 32.5; 95% CI: 16.3; 71.9), for squamous-cell lung cancer (ERR/Gy = 3.1; 95% CI: 0.3; 9.1)
- liver cancer risk and plutonium exposure was described under a linear-quadratic (LQ) function, Hepatocellular cancer was the most frequently observed type of liver cancer associated with internal plutonium exposure, and hemangiosarcomas were exclusively observed only at high internal plutonium doses (94 Gy).
- For malignant neoplasms of bone and associated connective tissues : no clear trend , but an excess observed in unmonitored females, that worked in the early years, « in the most hazardous plutonium production facility »

Low protracted exposure

- Mayak workers
 - Mean external dose (Gy) 0.54
 - Mean internal plutonium dose
 - to the lung (Gy) : 0.15
 - to liver : 0.31



Uncertainties

- Imprecision in urine measurements; urine samples available only for 30% of the cohort, started since 1971
- Uncertainties in when plutonium exposure occurred and form of plutonium
- Uncertainties in biokinetic models and parameter values used to estimate deposition and clearance in organs of the body
- Models can only approximate behavior of plutonium in a given individual
- Follow-up : migration out of Ozioursk: 41 %

Discussion

- Should ICRP calculate a risk detriment from alpha emitters ?
- Consider RBE through epi studies,
- Based on presently available data, or wait for further input ?
- Based only on lung cancer risk ?
- Risk other than cancer ? Cardiovascular ?
- It is a complex approach: different age distribution, sex, time dependancy, co-factors, models to be used
- Historical incidence rates, different backgrounds..... would need an international expertise on detriment calculations, and probably more research on methodology to be applied
- It is an important step, as radiation protection is mainly based on detriment approach