



Quantitative assessment of the childhood leukemia risks related to natural background radiation in France, exploring the impacts of uncertainty in risk models and parameters

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May chronic exposure to low doses rate of ionizing radiation (e.g., as those delivered by Natural Background Radiation) be a cause of childhood leukemia ?

☞ An important topic for radiation protection

◆ **Natural Background Radiation (NBR)** constitutes the **major source** of chronic exposure to ionizing radiation (IR) for most of the world population (2.4 mSv/year; UNSCEAR^(*), 2008)

◆ Three components contribute to **90% of the effective dose** delivered by NBR

- Radon gas (^{222}Rn and ^{220}Rn) and its decay products
- Terrestrial gamma rays (TGR)
- High energy cosmic ray particles

◆ **Positive association** between radon exposure and leukemia incidence

- Some, though not all, ecological studies (Evrard et al., 2006; Laurier et al., 2001)
- A case-control study in Denmark (Raaschou-Nielsen et al., 2008) but limited statistical power

◆ **Positive association** between exposure to gamma rays (TGR+ cosmic rays) and childhood leukemia incidence

- A sufficient size record-based case control-study in Great Britain (Kendall et al., 2013)

(*) United Nations Scientific Committee on the Effects of Atomic Radiation

- ◆ Additional well-designed epidemiological studies in progress BUT years to decade of observations required to reach an adequate statistical power

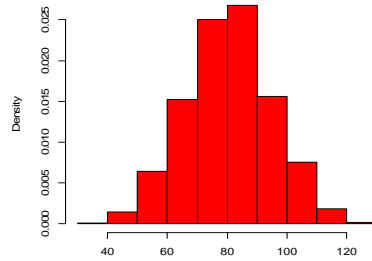
- ◆ Alternative approach: Quantitative Risk Assessment (QRA) (NRC 2009)
 - Preliminary and short-term replies on the magnitude of the potential effects of NBR on childhood leukemia

Main assumption : Radiation-related excess leukemia risks, estimated from an *evidentiary population* - classically, the data of the Life Span Study (LSS) of Hiroshima and Nagasaki A-bomb survivors - can be transposed to the specific context of exposure to NBR in a given *target population*

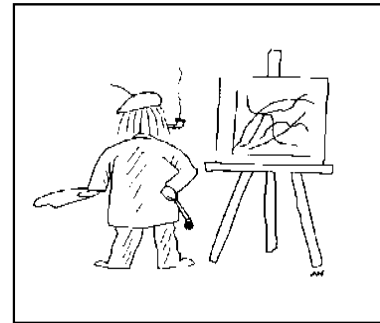
- Applied in Great Britain (before Kendall et al. 2013) : 15 to 20% of the cases of childhood leukemia (between 0 to 14 years old) potentially attributable to NBR (Little et al. 2009; Wakeford et al., 2009)

What about in metropolitan France?

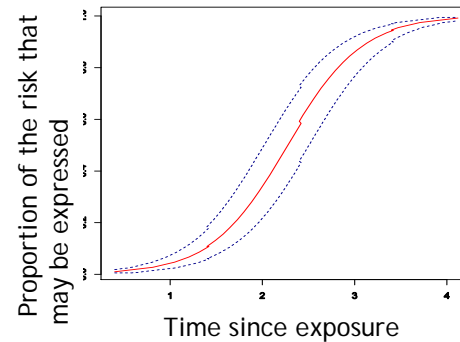
◆ Practice of QRA often ignore potentially important sources of uncertainties...



Uncertainty by ignorance about the model parameters



Model selection uncertainty



Uncertainty by ignorance in minimal latency period between exposure to IR and the beginning of expression of the risk

Aims of the work

- ◆ To explore the potential impacts of uncertainty in dose-response models, risk coefficients and minimal latency period between exposure to NBR and the expression of risk when predicting the percentage of childhood leukemia in France potentially due to 3 components of NBR - radon, cosmic rays and TGR
- ◆ To propose a Bayesian QRA approach applied to chronic exposures to NBR to account for several sources of uncertainty in the risk assessment process
- ◆ First QRA of childhood leukemia and NBR conducted to date in France

The *evidentiary population*

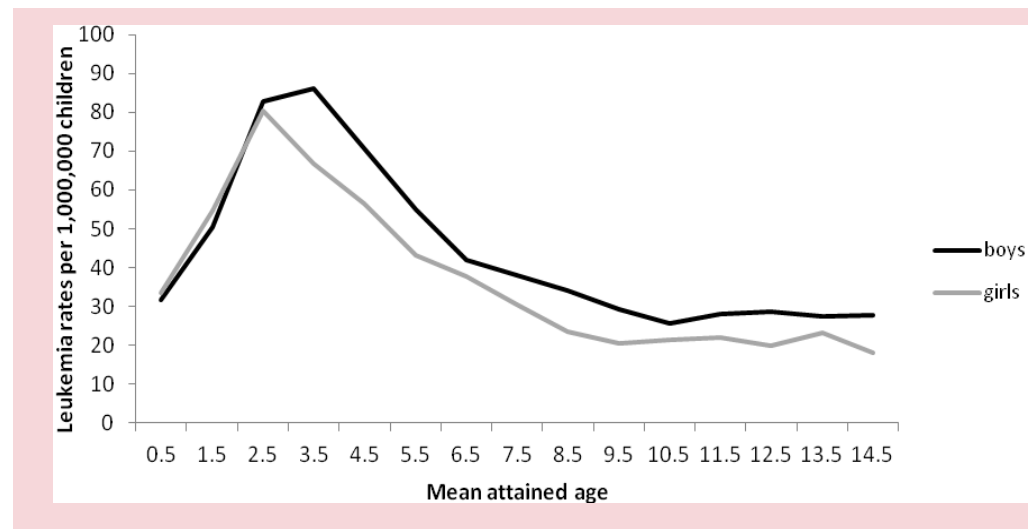


◆ Mortality dataset from the latest Life Span Study (LSS) cohort (provided by the Radiation Effects Research Foundation, Hiroshima, Japan)

- 86,611 survivors of the atomic bombings of Hiroshima and Nagasaki over period 1950-2000
- 284 leukemia deaths
- Stratified data by city, sex, age at exposure, weighted colon dose category (in Sv), attained age, calendar time period... → 31,422 strata
- Stratum-average red bone marrow (RBM) doses (in Sv) corresponding to the DS02 dosimetric system (2002)

The *target population* (1)

- ◆ Childhood acute leukemia incidence rates in metropolitan France by sex and mean attained age (0-14 years old), period 1990-2004
(provided by the French National Registry of Childhood Blood Malignancies (INSERM - RNHE))



- 6784 childhood leukemia cases recorded in France during the study period

The *target population* (2)

◆ Average red bone marrow (RBM) equivalent doses (in mSv) received by fetuses, infants and children from radon, terrestrial gamma rays and cosmic rays in metropolitan France

	Radon	TGR	Cosmic rays	Total
In utero (9 month)	0.03 ^c	0.33 ^b	0.19 ^b	0.55
Infant (first year of life ^e)	0.29 ^a	0.61 ^d	0.35 ^d	1.24
Child (yearly ^f)	0.34 ^a	0.55 ^d	0.31 ^d	1.21
Cumulated (in utero - 12.5 years)	4,40	7,54	4,26	16,31
% of cumulated dose (in both cases)	27	46	26	100

a. Estimated as in ([Kendall and Smith, 2005](#));

c. Estimated as in ([Kendall and Smith, 2002](#));

e. mean age at exposure =0.5 y;

b. Estimated as in ([Saito et al., 1990](#))

d. Estimated as in ([Petoussi et al., 1991](#))

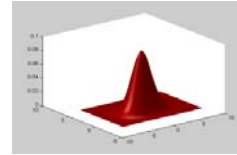
f. yearly dose from age at exposure 1.5 to 12.5 years

The *dose-response models*

- ◆ Five recently published risk models for radiation-related leukemia
- ◆ Poisson models to describe the number of leukemia deaths per stratum with :
 - Linear-quadratic structures for the Excess Relative Risk (ERR) or the Excess Absolute Risk (EAR) due to RBM dose
 - Baseline Risks (h^0) and Excess Risks (ER) of leukemia death depending on sex (s) and/or average attained age (a) and/or average age at exposure (e)
 - Excess Risks (ER) also depending on stratum-average RBM doses

ERR models	Number of parameters	EAR models	Number of parameters
ERR.UNSCEAR (2006)	10	EAR.UNSCEAR (2006)	11
ERR.Little (2008)	11	EAR.Preston (2004)	23
		EAR.Schneider (2009)	13

Step 1: Bayesian inference from the *evidentiary population* for characterizing the uncertainty distributions of risk parameters

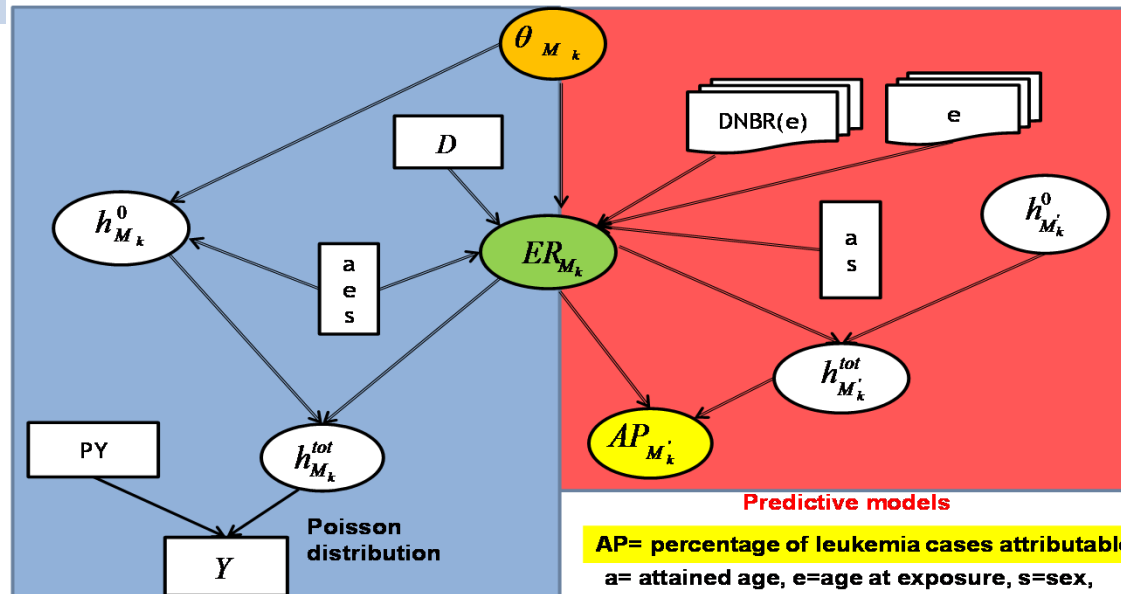


Step 2: Risk predictions in the *target population*

◆ Deriving predictive distributions by propagating the uncertainty in the risk parameters

- ◆ MCMC algorithm
- ◆ Flat normal priors

LSS, the whole population, flash exposure → France, children, chronic exposure



UNSCEAR 2006
generalized excess risk
models

Predictive models

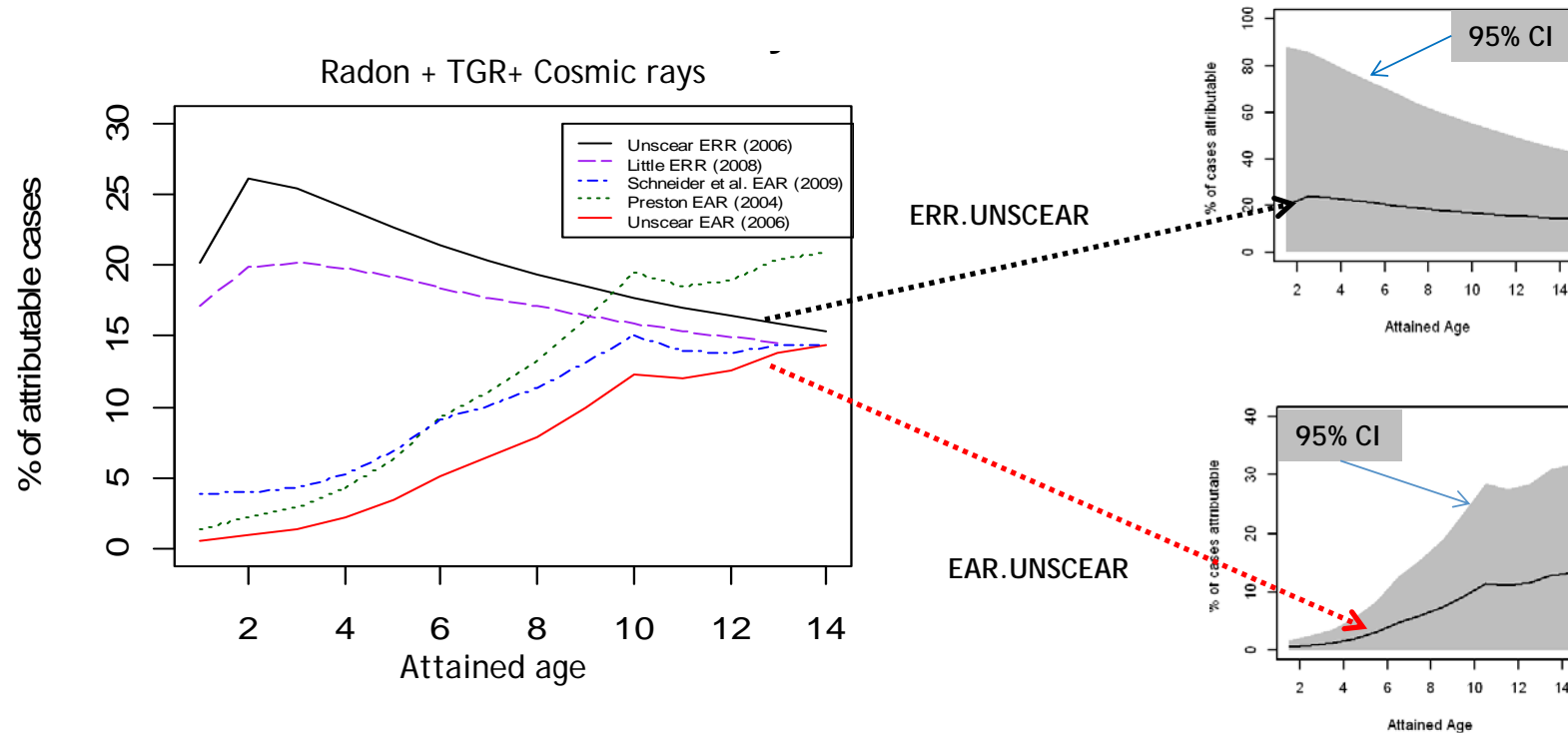
AP= percentage of leukemia cases attributable

a= attained age, e=age at exposure, s=sex,
D=dose, DNR=Dose due to NR, PY= Person-Years
ER= ERR or EAR

$$h_{M_k}^{tot} = h_{M_k}^0 + EAR_{M_k}$$

$$h_{M_k}^{tot} = h_{M_k}^0 \times (1 + ERR_{M_k})$$

- ◆ Posterior predictive medians and 95% credible intervals (95%CI) of the percentage of male cases of childhood leukemia potentially attributable to NBR over period 1990-2004 in France (2 years minimal latency period)



- ◆ Contrasted results → Substantial uncertainty attached to model specification
- ◆ The ERR.UNSCEAR (2006) and EAR.UNSCEAR (2006) models seem to provide a synthetic range for variation of the results according to model choice
- ◆ 95% credible intervals (95%CI) for predictions are very large

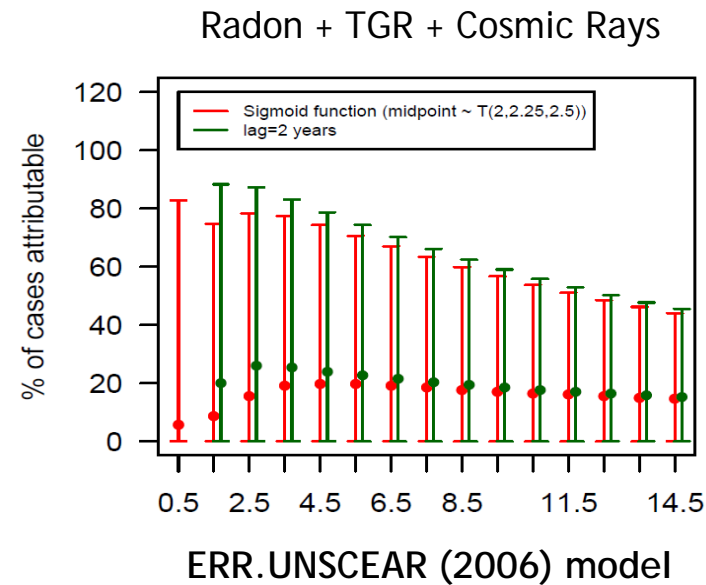
- ◆ Percentages of childhood leukemia cases with related 95% CI potentially attributable to radon, terrestrial gamma and cosmic rays over period 1990-2004 in metropolitan France and over childhood (from 0 to 14 years old) according to the UNSCEAR 2006 risk models
(2 years minimal latency period)

Components of natural radiation Predictive model type	Radon		terrestrial gamma rays		cosmic rays		all 3 exposures together	
	ERR	EAR	ERR	EAR	ERR	EAR	ERR	EAR
Males								
% of attributable cases								
Posterior predictive median)	5.5	1.4	11.3	2.4	6.9	1.4	20.5	5.2
95% CI	(0-36.1)	(0-3.6)	(0-53.6)	(0-6.2)	(0 -42.0)	(0 - 3.5)	(0 - 67.6)	(0 -13.3)
Females								
% of attributable cases								
Posterior predictive median	5.3	0.9	11.4	1.6	6.9	0.9	20.4	3.4
95% CI	(0-36.2)	(0-2.4)	(0-54.6)	(0-4.2)	(0-43.2)	(0 - 2.4)	(0-68.0)	(0-9.0)
Criterion for model selection							BIC: 2801.8	BIC: 2817.7

- ◆ ERR.UNSCEAR (2006) provides the best fitting performances to the LSS dataset
- ◆ Bayesian point predictions suggest that a sizeable proportion (~20%) of childhood leukemia cases might be attributable to radon, TGR and cosmic rays in France
- ◆ BUT again 95% credible intervals (95%CI) for predictions are very large

Impact of uncertainty on the minimal latency period

- ◆ Classical assumption : 2-years minimal latency period between exposure to NBR and the expression of leukemia risk (—●— = 95%CI)
- ◆ Berrington de Gonzales et al. (2012) : Smoothed increase in the expression of the risk according to time since exposure + uncertainty in the minimal latency period (—●— = 95%CI)



- ◆ Over childhood : 16% (95%CI: 0-66%) for ERR. UNSCEAR

- ◆ Point predictions suggest that a sizeable proportion of childhood leukemia cases (~16-20% according to the ERR.UNSCEAR 2006 model) might be attributable to radon, TGR and cosmic rays in France
 - So far, consistent with UK findings (Wakeford et al. 2009)
 - BUT 95% credible intervals for predictions appear to be very large
 - Results valuable provided that UNSCEAR 2006 risk models can be transferred

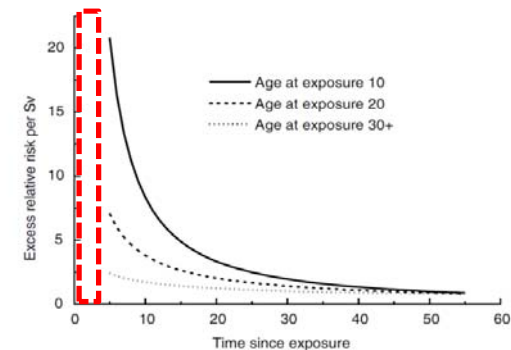
☞ Point predictions must be interpreted cautiously !

- ◆ Other sources of uncertainty could be accounted for explicitly :
 - Uncertainty on the equivalent doses received by the RBM in France
 - Model uncertainty

☞ The Bayesian approach: a rigorous and coherent way to integrate several sources of uncertainty in a Quantitative Risk Assessment

◆ Important limitations of the LSS to help predicting childhood leukemia due to Natural Background Radiation

- Dose level extrapolation
- Dose rate extrapolation : acute exposure to A-Bomb radiation VS chronic exposure to NBR
- Age group extrapolation : specific uncertainty in the LSS for the magnitude of the effects at the youngest ages and shortest time since exposure periods (<5 y)



- Further epidemiological studies in children are needed
- Data acquisition in progress in France (Geocap Project)

Thank you for your attention !

☞ Laurent O., Ancelet S. et al. (2013) Potential impacts of radon, terrestrial gamma and cosmic rays on childhood leukemia in France : a quantitative risk assessment, *Radiation and Environmental Biophysics*, Volume 52(2), pp 195-209