United Nations Scientific Committee on the Effects of Atomic Radiation

ELECTRONIC ATTACHMENT

MODELS OF EXCESS RELATIVE RISK WITH MODIFYING EFFECTS

UNSCEAR 2019 Report, Annex B, Lung cancer from exposure to radon

Contents

Acknowledgements

The Committee acknowledges the work done by L. Tomášek (Czech Republic) in developing model 2 with contributions from P. Demers (Canada) and N. Fenske (Germany) in conducting the calculations presented in this attachment.

Notes

I. MODELS OF EXCESS RELATIVE RISK WITH MODIFYING EFFECT OF EXPOSURE RATE

1. The modifying effects of age, time since exposure and exposure rate were found to be important factors that influence the effect of lung cancer risk on cumulated exposure to radon progeny. The modifying effect, in the BEIR VI models, was estimated for categories of exposure rate calculated for each subject as mean exposure rate, i.e. cumulated exposure in working level month (WLM) divided by cumulated duration of exposure in months [N1]. As annual exposure rates are quite different during exposure history, particularly for long-term employment (being mostly higher in the early periods and lower later) this approach mixes contribution of higher and lower exposure rates in a single category of mean exposure rate when miners were exposed for longer periods. Therefore, another approach was suggested to reflect the actual different exposure rate in each year of exposure. In this approach total cumulated exposure is modelled as two cumulated exposures resulting from low and high annual exposure rates W_L and W_H. The dependence of risk on exposure is calculated in relation to cumulated exposure from low and high annual exposure rates. For miners exposed only at high exposure rates, the contribution to low cumulated exposure would be zero, and similarly for miners exposed at only low exposure rates, the contribution to high cumulated exposure would be zero. Such patterns of exposure, however, are not typical. Quite a large proportion of miners experienced both types of exposure. The suggested model to calculate the excess relative risk (ERR) is:

$$ERR = b_L W_L + b_H W_H \qquad \text{(Model 1)}$$

where b_L and b_H are crude coefficients of ERR per WLM from low and high annual exposure rates. This model can be further improved by including modifying factors of attained age (A) and time since exposure (T):

$$ERR = (b_L W_L + b_H W_H)\ \phi(A)\ \theta(T) \qquad \text{(Model 2)}$$

where $\phi(A)$ and $\theta(T)$ are stepwise functions similar to the BEIR VI age-concentration model. The categories of attained age were <55, 55–64, 65–74, 75+ years, and the categories of time since exposure were 5–14, 15–24, and 25+ years.

2. The above models were applied to the combined 11 cohort studies included in BEIR VI [N1] and to the Czech, Ontario and Wismut cohorts. The percentage of person–years below 0.5 WL to all persons exposed were calculated and presented in table 1. In addition to numbers of person–years and lung cancers, table 1 contains information on exposures calculated separately for high (>0.5 WL) and low (<0.5 WL) exposure rates as well as the proportion of person–years with low exposure rate. This indicator is substantial for reliable estimates of ERR per WLM from low exposure rates in each study. High proportions are in European cohorts (France, Germany and Sweden) and in North America cohorts (Newfoundland, New Mexico, and Ontario).

Table 1. Percentage of person–years <0.5 WL to all exposed in BEIR VI (11 studies), Czech, Ontario and Wismut cohorts

Study	*Person–years <0.5 WL (%)*	*Number of lung cancers*	*Number of person–years*	*W* [a] *(WLM)*	W_L [b] *(WLM)*	W_H [c] *(WLM)*
BEIR VI (11 studies)	31	2 864	1 180 988	140.5	8.3	210.6
Beaverlodge	26	65	114 384	11.4	3.2	29.2
China	15	975	190 988	253.7	10.6	332.5
Colorado	1	377	89 654	605.1	2.1	677.8
Czechoslovakia	10	705	106 946	188.4	8.9	192.2
France	77	45	43 959	51.6	15.3	69.5
New Mexico	47	69	58 648	102.4	5.9	163.4
Newfoundland	44	147	58 571	248.0	3.6	515.2
Ontario	41	291	380 691	23.9	3.2	34.2
Port Radium	5	57	51 850	136.9	1.0	257.9
Radium Hill	31	54	51 853	3.6	3.7	10.0
Sweden	88	79	33 444	77.5	38.3	63.5
Czech	63	1 161	315 709	54.9	6.8	124.7
Ontario	53	1 246	1 005 194	24.2	4.4	32.7
Wismut	64	3 942	2 332 008	201.8	10.7	460.6

[a] W = mean cumulative exposure weighted by person–years.
[b] W_L = mean cumulative exposure for <0.5 WL weighted by person–years.
[c] W_H = mean cumulative exposure for >0.5 WL weighted by person–years.

3. Crude estimates of ERR per WLM from low and high exposure rates are given in table 2 for model 1 applied to the combined BEIR VI cohorts and the Czech, Ontario and Wismut cohorts.

Table 2. Estimated excess relative risk per WLM for low (<0.5 WL) and high (>0.5 WL) exposure rates in BEIR VI (11 studies), Czech, Ontario and Wismut cohorts

Study	*ERR per 100 WLM (standard error)*	
	Exposure rate <0.5 WL	*Exposure rate >0.5 WL*
BEIR VI (11 studies)	4.18 (0.88)	0.40 (0.04)
Czech	1.69 (0.97)	0.95 (0.15)
Ontario	3.52 (0.82)	0.72 (0.12)
Wismut	2.00 (0.40)	0.42 (0.05)

4. Parameter estimates for model 2 are given in table 3 along with the excess absolute risk (EAR) per 10^4 PY WLM calculated as

$$\text{EAR per } 10^4 \text{ PY WLM} = r_0 \text{ ERR per WLM}$$

where r_0 is background rate.

Table 3. Estimated excess relative risk per 100 WLM and excess absolute risk per 10^4 PY WLM derived using model 2 for the BEIR VI (11 studies), Czech, Ontario and Wismut cohorts as well as observed lung cancer rates and modification factors for time since exposure and exposure rate

Parameters	*BEIR VI (11 studies)*	*Czech*	*Ontario*	*Wismut*	*p-value* [a]
Age specific ERR per 100 WLM (standard error)					
<55	12.71 (3.01)	7.22 (3.75)	9.36 (3.67)	3.70 (0.83)	0.206
55–64	4.22 (0.98)	2.72 (1.27)	2.92 (1.06)	1.79 (0.35)	0.408
65–74	1.47 (0.44)	1.28 (0.64)	1.06 (0.52)	1.25 (0.24)	0.962
75+	1.17 (0.75)	1.05 (0.75)	1.11 (0.85)	1.18 (0.23)	0.996
Age specific EAR per 10^4 PY WLM					
<55	0.39	0.30	0.15	0.05	
55–64	1.57	0.91	0.58	0.28	
65–74	1.17	0.98	0.44	0.48	
75+	0.72	0.85	0.43	0.67	
Age specific observed lung cancer rate [b] (background)					
<55	100 (31)	152 (41)	25 (16)	36 (13)	
55–64	766 (372)	738 (335)	264 (197)	327 (155)	
65–74	1 152 (799)	1 371 (768)	474 (415)	628 (381)	
75+	858 (612)	1 365 (807)	448 (385)	784 (567)	
Time since exposure [c]					
<15	1.00	1.00		1.00	
15–24	0.96 (0.09)	0.89 (0.14)		0.88 (0.03)	0.383
25+	0.71 (0.07)	0.57 (0.09)		0.67 (0.07)	0.937
Exposure rate [c]					
<0.5 WL	1.00	1.00	1.00	1.00	
>0.5 WL	0.10 (0.02)	0.88 (0.49)	0.36 (0.11)	0.21 (NA)	

[a] *p*-value for parameter differences between studies.
[b] Incidence of lung cancer per 100,000 persons.
[c] Relative effect (standard error).

5. As shown in table 4, risk coefficients are generally higher, particularly in younger age groups when applying the model 2 in comparison to the BEIR VI model. The higher risk coefficients are also reflected in higher lifetime excess absolute risks (LEAR) (table 5).

Table 4. Estimated age specific excess relative risk per 100 WLM derived using model 2 and BEIR VI model as well as modification factors for time since exposure and exposure rate

Parameters	*BEIR VI (11 studies)*		*Czech*		*Wismut*	
	BEIR VI model	*Model 2 (standard error)*	*BEIR VI model*	*Model 2 (standard error)*	*BEIR VI model*	*Model 2 (standard error)*
Age specific ERR per 100 WLM						
<55	7.68	12.71 (3.01)	6.47	7.22 (3.75)	2.31	3.46 (0.99)
55–64	4.38	4.22 (0.98)	1.81	2.72 (1.27)	1.11	1.61 (0.43)
65–74	2.23	1.47 (0.44)	1.42	1.28 (0.64)	0.76	1.11 (0.31)
75+	0.69	1.17 (0.75)	1.36	1.05 (0.75)	0.74	1.12 (0.35)
Time since exposure [a]						
<15	1.00	1.00	1.00	1.00	1.00	1.00
15–24	0.78	0.96 (0.07)	0.77	0.89 (0.14)	0.79	0.74 (0.10)
25+	0.51	0.71 (0.09)	0.41	0.57 (0.09)	0.54	0.56 (0.09)
Exposure rate [a]						
<0.5 WL	1.00	1.00	1.00	1.00	1.00	1.00
>0.5 WL	0.11–0.49	0.10 (0.02)	0.63–1.29	0.88 (0.49)	0.16–0.61	0.22 (0.05)

[a] Relative effect (standard error).

Table 5. Estimated lifetime excess absolute risk derived using model 2 and BEIR VI model for additive, multiplicative and mixed baseline risks

Baseline risk assumption	*LEAR [a] per 10^4 persons per WLM (standard error)*			
Model 2				
	BEIR VI (11 studies)	*Czech*	*Ontario*	*Wismut*
Additive baseline risk (EAR)	21.0 (4.4)	13.4 (3.2)	11.8 (3.0)	5.4 (1.1)
Multiplicative baseline risk (ERR)	8.7 (1.8)	5.6 (1.3)	8.3 (2.1)	4.0 (0.8)
Mixed baseline risk [b]	16.9 (3.6)	10.8 (2.6)	10.7 (2.7)	4.9 (1.0)
BEIR VI model				
	BEIR VI (11 studies)	*Czech*	*Eldorado*	*Wismut*
Additive baseline risk (EAR)	17.7 (4.1)	11.9 (3.1)	17.2 (6.9)	4.0 (0.9)
Multiplicative baseline risk (ERR)	7.0 (1.6)	5.0 (1.3)	9.6 (3.8)	3.0 (0.7)
Mixed baseline risk [b]	14.2 (3.3)	9.6 (2.5)	14.7 (5.9)	3.6 (0.9)

[a] LEAR per WLM was calculated for the ICRP Asia and Euro-American male population [I1] up to 95 years of age with an exposure scenario of 2 WLM per year from 18 to 64 years of age. A lag time of 5 years was assumed.
[b] Average weighting of 2/3 additive and 1/3 multiplicative baseline risk estimates as applied by ICRP [I1].

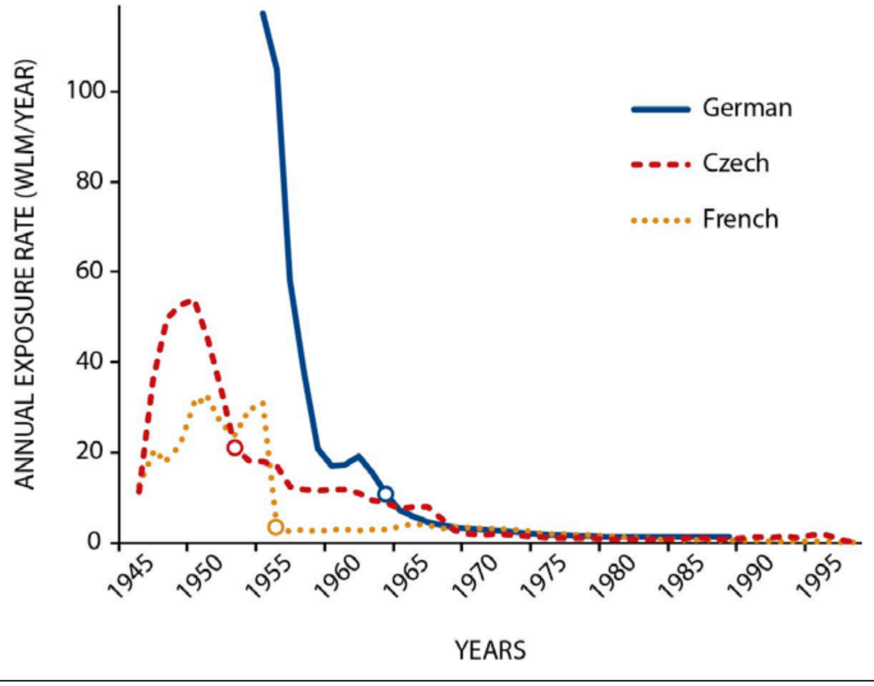
II. MODELS OF EXCESS RELATIVE RISK WITH MODIFYING EFFECT OF PERIOD OF EXPOSURE

6. Presented in this section are models developed within the Alpha-Risk project [A1, T1]. The focus of Alpha-Risk was "Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment". Table 6 shows summary information of the three European cohorts of uranium miners (Czech, French and German) included in the Alpha-Risk project. The project evaluated modifying factors such as time since exposure, attained age, exposure rate, and age at exposure. Quantitative differences exist in the dependence of risk coefficients on quality of exposure estimates. The project aimed to verify these modifying effects and to estimate the risk from low exposure at low exposure rates, which are also characterized by high-quality exposure estimates. The project analyses were realized in three large cohorts of European miners, where large proportions of exposure were based on extensive measurements and personal monitoring. Mean annual exposures in the three cohorts were higher in earlier periods, whereas in later periods the levels were lower and similar in the cohorts (figure I).

Table 6. Summary information for studies included in the Alpha-Risk project

Cohorts	*Period of follow-up*	*Number of miners*	*Person–years*	*Lung cancers*
Czech	1952–1999	9 970	261 984	921
French	1946–1999	5 086	152 884	159
German	1955–1998	35 084	901 681	458
Joint Alpha-Risk		50 140	1 316 549	1 538

Figure I. Mean annual exposure rates (WLM/year) of the cohorts involved in the Alpha-Risk project [A1, T1]



7. The effect of radon exposure was investigated with model 3 calculating the relative risk (RR) as

$$RR = 1 + (b_1 W_1 + b_2 W_2) \exp(t(TME-20)/10) \exp(a(AME-30)/10) \qquad \text{(Model 3)}$$

where W_1 and W_2 are exposures cumulated in different calendar periods reflecting level of exposure estimates. Figure I shows that the cut points for calendar periods were set so that the model had the largest difference in deviances in comparison to a model with one exposure window (Czech 1953, French 1956, German 1964). Variables TME and AME denote time since median exposure and age at median exposure. Estimated parameters b_1 and b_2 are ERRs per WLM corresponding to different calendar periods of exposure, and parameters t and a describe modifying effects of age at exposure and time since exposure (table 7).

Table 7. Excess relative risk per WLM for two periods of exposure and modifying effects of age at exposure and time since exposure included in the Alpha-Risk project (model 3)

Model parameters [a]	*Estimate value*	*Standard error*
Czech cohort		
ERR/WLM (recent period ≥1953)	0.0505	0.0098
ERR/WLM (earlier period <1953)	0.0192	0.0045
Time since exposure [a]	0.418	0.066
Age at exposure [a]	0.610	0.095
French cohort		
ERR/WLM (recent period ≥1956)	0.0395	0.0202
ERR/WLM (earlier period <1956)	0.0076	0.0059
Time since exposure [a]	0.522	0.208
Age at exposure [a]	0.558	0.263
German cohort		
ERR/WLM (recent period ≥1964)	0.0256	0.0065
ERR/WLM (earlier period <1964)	0.0062	0.0015
Time since exposure [a]	0.541	0.095
Age at exposure [a]	0.822	0.139
Joint Alpha-Risk cohort		
ERR/WLM (all studies, recent periods)	0.0379	0.0051
ERR/WLM (Czech, earlier period <1953)	0.0161	0.0033
ERR/WLM (France, earlier period <1956)	0.0090	0.0055
ERR/WLM (Germany, earlier period <1964)	0.0074	0.0016
Time since exposure [a]	0.461	0.049
Age at exposure [a]	0.681	0.071

[a] Model parameters represent relative changes per decade of time and age, respectively.

8. Although estimated parameters in the joint model were not statistically different from cohort specific models (χ^2=7.0; p=0.321), the predicted lifetime risk was higher for the Czech cohort and lower for the German cohort (table 8). As the risk model depends on age, the age distribution of observed cases is an important consideration. This is illustrated in table 9, where the observed lung cancer rates in younger ages are higher in the Czech cohort. Accordingly, the observed rates are higher because of higher exposure. Therefore, it is necessary to consider background rates, i.e. hypothetical rates, estimated for zero exposure in the given model.

Table 8. Lifetime excess absolute risk per 10,000 persons per WLM according to model 3 used in table 7 for multiplicative baseline risks

Cohort	*LEAR[a] per 10^4 persons per WLM (standard error)*
Czech	13.2 (2.5)
French	7.9 (4.0)
German	7.7 (1.7)
Joint Alpha-Risk	9.1 (1.1)

[a] LEAR per WLM was calculated for the ICRP Asia and Euro-American male population [I1] up to 95 years of age with an exposure scenario of 2 WLM per year from 18 to 64 years of age. A lag time of 5 years was assumed.

Table 9. Observed (background) lung cancer rates per 100,000 persons by age groups in cohorts involved in the Alpha-Risk project

Age	*Czech cohort*	*French cohort*	*German cohort*
<45	44 (10)	9 (5)	7 (4)
45–54	403 (91)	78 (45)	72 (40)
55–64	1 019 (277)	244 (162)	275 (168)
65–74	1 475 (584)	436 (336)	633 (433)
>75	1 228 (679)	578 (513)	719 (560)

References

A1 Alpha-Risk Consortium. The Alpha-Risk project. Eur Parliament Mag 260 (January): 10-11 (2008).

I1 ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Annals of the ICRP 37(2-4). International Commission on Radiological Protection, Elsevier Ltd., 2007.

N1 NRC. Health effects of exposure to radon. Committee on Health Risks of Exposure to Radon, BEIR VI. National Research Council, National Academy Press, Washington, D.C., 1999.

T1 Tirmarche, M., D. Laurier, F. Bochicchio et al. Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment. Final scientific report in the frame of the European project “Alpha Risk” No. 516483, period 2005-2009. EUR 24599. 2010.