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## **$\alpha$ -Risk**

Quantification of cancer and non-cancer risks  
associated with multiple chronic radiation exposures:  
Epidemiological studies, organ dose calculation and risk assessment

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**Quantification of cancer and non cancer risks associated with multiple chronic radiation exposures: Epidemiologic studies, organ dose calculation and risk assessment.**

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## Introduction

In radiation epidemiology many studies have been carried out to quantify the effects of external photon exposure, based on the Japanese A-bomb survivors, on patients with medical exposures and on nuclear workers. Today, the main issues to be considered in radiation protection are potential long-term health effects after exposure to other radiation types, like alpha-emitters. The general public daily inhales, at relatively low levels, alpha emitters that arise through domestic radon decay exposure. Various subgroups of nuclear workers are also exposed to alpha emitters during their occupational life. Only few studies are able to provide information on long term health effects after exposure to plutonium (Pu) and uranium (U) isotopes.

## Objectives

The objective of the AlphaRisk project is to improve the quantification of long-term health risks, cancer and non cancer, associated to chronic internal contamination by alpha-emitters. It regrouped major studies in Europe that are able to consider chronic internal exposure in large populations and to evaluate associated long-term health effects. Advantage has been made of already existing European collaborations that worked successfully during previous EU contracts in order to strengthen expertise and increase statistical power for these low risk studies. Various complementary fields of expertise were involved: epidemiology, organ specific dosimetry, statistical modelling, and accounting for uncertainty in risk assessment. New studies were launched in the field of occupational exposure, by focusing on those workers for whom precise individual information on internal exposure has been registered during their occupational life. Collection and validation of these data made it possible to plan future large cohorts able to answer the question of a possible link between a disease and a specific exposure (example: uranium under different chemical forms). A case-control study realized during this program focused mainly on lung cancer and leukaemia risk.

The results of these studies were expressed as excess risk coefficients per unit of exposure or per organ dose and modelled in relation to time-dependent variables. The possibility of taking into account co-factors like occupational chemicals, tobacco, gender, age at exposure, and attained age was a major component of these joint analyses based on a large amount of data collected under the commonly shared study protocol.

It was possible to compare the calculated specific risk per organ dose with the more common risk per unit of exposure characterised by environmental measurements. The final objective of this large collaboration was the discussion of more or less sophisticated risk models as a tool for prediction of lifelong risks and for application to populations that differ from those directly involved in the present cohort or case-control studies. The comparison of these risk factors with those from populations exposed solely to external exposure was enhanced through this "organ dose approach".

## Description of the research performed

WP1 - Cohorts of uranium miners investigated many relevant topics in the field of epidemiological studies of miners. A complex and multi-directional research project has been constituted and, thanks to the very successful collaborations that were developed in the frame of WP1 and with WP5, all objectives were achieved. This collaborative work allowed studying more thoroughly health effects of radon and more generally alpha emitters, and notably the modifying factors of these effects. It led also to very innovative developments in the production of new knowledge, especially regarding the calculation of organ doses for miners

WP2 - Indoor radon studies: A specific format allowing a data base for a future joint analysis of the worldwide and published data on lung cancer and domestic exposure was realized and validated. Joint analysis is in progress and close to publication. In parallel, a review of new data sets and published papers on repeated radon measurements in different years in the same dwellings was completed. This review allowed evaluating radon exposure uncertainty in residential epidemiological studies and correcting for the bias produced by such exposure uncertainty. Two new and unpublished European data sets were collected and analysed, regarding dwellings in Italy and Switzerland. Published data of case control studies on lung cancer in Europe, in China and in North America were considered and compared with annual variations observed during this project, in order to evaluate the possible impact on corresponding risk estimates.

WP3 - Nested case-control studies among nuclear workers: The aim of this WP was to assess the risk of lung cancer and leukaemia mortality in relation to internal exposure to specific radionuclides (uranium and plutonium) amongst workers in the nuclear industry, with appropriate adjustments for tobacco smoking habits and occupational external radiation doses. The work consisted in the conduct of two case-control studies, of lung cancer and leukaemia respectively, nested within appropriate cohorts from the International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry. The case-control design allowed detailed dose reconstruction as well as the collection of individual data on potential confounders.

WP4 - Cohorts of nuclear workers with internal exposure: The primary objective of this WP was to assess the feasibility of a future joint cancer and non-cancer mortality study of the cohorts of BNFL-UK (Sellafield and Springfields) and French (CEA-AREVA) plutonium and uranium workers. An outline Research Study Protocol for a joint cohort study was written as well as a methodology for reconstructing internal doses and tobacco smoking history. This work highlighted the feasibility and pertinence of such a large joint cohort study with a long term follow-up.

WP5 - Organ dose: This WP aimed at calculating estimates of individual absorbed doses to specific target tissues (lung regions, red bone marrow, kidney, liver) and associated uncertainties in relation to characteristics of individuals (attained age, smoking habits). Doses estimated under this WP were then used for the epidemiological studies of uranium miners under WP1. Moreover all uncertainties affecting these doses were quantified in order to select the "best" models by comparing different modeling approaches.

WP6 - Integration of results: This WP involved an analysis of combined case-control data on uranium miners in 3 European studies (in the Czech Republic, France and Germany) and a comparison of lung cancer risk estimates across this analysis, the BEIR VI (1999) analysis of miner studies and the combined analysis of 13 European

residential radon case-control studies (Darby et al, 2005, 2006). From this comparison, exposure-response models were developed and factors that may modify this relationship such as smoking, time since exposure and age were investigated. The link between the exposure measures from radon progeny in mines (expressed in terms of Working Level Months, WLM) and long-term average radon concentration in homes (expressed in Bq/m<sup>3</sup>) was also addressed. Furthermore, lifetime lung cancer risks due to radon exposure were assessed based on various risk models and exposure scenarios (e.g. concerning the impact of radon mitigation of homes).

## Main achievements

- Construction of a joint database combining the three European cohorts of uranium miners, including individual information on more than 50,000 miners with a mean follow-up duration of more than 26 years for analysis of mortality risk. An excess of lung cancer risk was confirmed using this new dataset. Excesses and trends with cumulative exposure were also observed for leukaemia, and in one study for cerebro-vascular diseases. Kidney cancer was observed in excess in two of the three cohorts.
- Refinement of the relationship between lung cancer risk and radon exposure. Considering only periods with a good quality of exposure and low exposure rates, the resulting lung cancer risk coefficients were very coherent between the three cohorts. The analysis confirmed the importance of modifying factors of the exposure-risk relationship, particularly the effects of time since exposure, attained age, and exposure rate at high levels of exposure.
- Three case-control studies respectively nested in the three cohorts were performed. Altogether, the three studies include more than 1000 cases and 2400 controls. In the three studies, the results showed that adjustment on smoking status only slightly modified the relationship between radon exposure and lung cancer risk. Thus smoking seems no major confounder for the cohort studies. The results were compatible with a sub multiplicative interaction between radon exposure and smoking. The persistence of a significant association between radon exposure and lung cancer risk after taking into account smoking was confirmed using the floating absolute risk methodology.
- Application of the biologically-based two stage clonal expansion models for analyzing lung cancer mortality in the three European miner cohorts. All three studies indicated a highly significant action of radon on promotion. An action of radon on initiation was also observed, but significant only in the Czech and German studies.
- Characterization of measurement errors associated to radon exposure. This work permitted a synthetic description of uncertainties in the three cohorts. Using a two stage clonal expansion model, the changes in parameters due to consideration of radon exposure uncertainties appeared of minor importance.
- Development of a projection method to account for the smoking behaviour of a miners' population in which this information cannot be obtained individually. This approach allowed analysing the German miners data with a biologically-based two-mutation carcinogenesis model, with a separate description of the effects of tobacco and radon-exposure histories.
- Assessment of absorbed organ specific doses associated to chronic exposures to radon gas, radon decay products, external gamma rays and long-lived radionuclides. The Alpha Miner software developed by WP5 allowed estimating absorbed and equivalent doses to lung, kidney, liver and red bone marrow (RBM) for each miner from the European joint cohort. Dose description illustrated the differences in the respective contribution of each source of exposure between organs (alpha and non alpha exposures). The analyses according to the organ dose showed a positive and significant dose-risk relationship for lung cancer and for leukaemia.
- Analysis of the risk of leukaemia associated to both occupational exposures (radon, gamma rays, long lived radionuclides) and X-ray examinations due to diagnostic examinations in a case-control study of former uranium miners in East Germany (377 cases and 980 controls). RBM absorbed doses were calculated using the Alpha Miner software. An elevated relative risk was seen in the dose category above 200 mGy.

Results also suggested a longer lag time between exposure and risk than classically considered for leukaemia.

- Review and comparison of different approaches to correct lung cancer risk in residential studies taking into account radon exposure uncertainties. A review of characteristics and results of epidemiological studies on lung cancer and residential exposure to indoor radon in order to highlight key issues relevant to the assessment of lifetime lung cancer risks from radon exposure. This review was used for the integration of results from residential and miner studies.
- Elaboration of the Common Study Protocol for comprehensive investigation of the lung cancer and leukemia risk related to internal exposure to uranium and plutonium amongst European nuclear workers. Cases and controls were selected from the 5 main European nuclear facilities (located in Belgium, France, and United Kingdom) where workers had a potential for internal incorporation of U and/or Pu. Demographic and risk factors information was collected for all eligible study participants. Internal doses from Pu and U were estimated using available bioassay data; doses to the bone marrow and to different regions of the lung were estimated using ICRP biokinetic models.
- Improvement of an existing software programme (IMBA Professional, Alpha Risk version) to allow a common dose reconstruction approach for all studies involved in the joint case-control study
- Development of a new software programme for the dosimetric uncertainty analyses, Uncertainty Analyser.
- Realisation of two joint case-control studies amongst European nuclear workers. In total, 561 lung cancer deaths and their 1,340 matched controls and 46 leukemia deaths and their 109 matched controls were included in the lung cancer and leukaemia case-control studies, respectively. Data collected for each study subject included demographic characteristics (e.g., sex and age), external radiation dose history, occupational history, as well as history of tobacco smoking, chest x-rays and chemical exposures. Risk analyses have been conducted and need further continuation.
- Assessment of the feasibility of the future joint cohort study of the French and British uranium and plutonium workers. All consents and permissions were obtained. Availability of epidemiology data were checked and indicates that data exist for around 10,000 French uranium workers in addition to the data already available for 10,000 BNFL uranium workers.
- Elaboration of the methodology to reconstruct smoking habits for BNFL workers using smoking information from occupational records. This methodology has been successfully applied to the 2,000 BNFL workers included in the case-control study.
- Elaboration of the common protocol to estimate plutonium and uranium organ specific doses in accordance with a methodology agreed by a European Union Internal Dosimetry Committee of experts.
- Comparison of radon-related lung cancer risks in the European case-control miner studies, BEIR VI data and European residential studies. The European case-control miner data and the BEIR VI analysis indicate that the excess relative risk (ERR) due to radon decreases significantly with increasing time since exposure. Allowing the ERR to depend on attained age does not improve the fit to the European miner data, although there are indications that the ERR decreases with increasing attained age. There is no evidence for such a trend in the European residential data. In both the European miner and residential data, the ERR due to radon for never-smokers is about twice the corresponding value for continuing smokers, but – as in the BEIR VI analysis - these differences are not statistically significant. Under both a multiplicative model and a sub-multiplicative model for the joint effects of radon and smoking on lung cancer risk, the excess absolute risk associated with radon is higher among current smokers and recent ex-smokers than among never-smokers.
- Development of a risk model as a modified version of the BEIR VI Exposure-Age-Concentration model, fitted to the European miner case-control data below 300 WLM. The model was designed to focus on low exposure rates. According to this model, for exposures 25 years or more ago, the ERR is just over 1/5th of that associated with exposures in the previous 5-24 years. The ERR decreases with increasing attained age. Both multiplicative and sub-multiplicative models for the joint effect of radon and smoking on the ERR were considered.



- Estimation of lifetime risks of radon-induced lung cancer. The lifetime risk estimates vary by around a factor of 2 between the various risk models considered: a model based on the European residential data provides the lowest risk estimates, while the BEIR VI-Exposure-Age-Concentration model gives the highest values. The lifetime risk estimates from the European miner models lie within this range. There is not much difference in the lifetime risk estimates for lung cancer death due to radon exposure between males and females.
- Assessment of the effect of smoking and radon: Under a multiplicative model for the joint association of radon exposure and smoking, the lifetime risk for radon-related lung cancer was highest for continuing smokers and lowest for never-smokers; the ratio of these risks is around 10-15. Those who quit smoking at age 50 years would decrease their lifetime radon-related lung cancer risk by around a half compared to continuing smokers with the same radon exposure, but the risk from radon for ex-smokers would be around a factor of 5-7 greater than that for never-smokers. Under a sub-multiplicative model for the joint effects of smoking and radon, the lifetime risk estimates are slightly smaller for continuing smokers and larger for never-smokers than the corresponding estimates under a multiplicative model. Under a sub-multiplicative model, the lifetime risk of radon-induced lung cancer is still higher for continuing smokers than for never-smokers (by around a factor of 5-7).
- Assessment of the effect of radon mitigation: Consideration of alternative exposure scenarios indicates that, even for persons aged in their 50s, radon migration of their homes could have a notable impact on their lifetime risk of radon-induced lung cancer mortality. Clearly, stopping smoking has a considerable impact in reducing lung cancer risks. Nevertheless - among continuing smokers, ex-smokers and never-smokers - measures to reduce radon exposure can also be important in reducing these risks.

## **Exploitation and dissemination of the results**

All these results were discussed in the frame of the Alpha-Risk project and have been detailed in 43 reports (deliverables). Most of these reports are still confidential as some further analyses are still ongoing and final results will be published in the scientific literature. Indeed, the project has already led to nearly 60 scientific communications and to 25 publications. More than 15 additional publications deriving from this work are expected in the next years.

These results will provide support for ongoing reflexions regarding the assessment of risks associated to alpha emitters and more generally in the field of radiation protection. In addition, the results also provide detailed information about the health status of uranium miners that are of high value in support to occupational epidemiology and protection of workers.

## **Perspectives**

The constructed combined studies (joint European cohorts of uranium miners, France-UK cohort of uranium workers, combined nested case-control studies amongst miners and nuclear workers) constitute large size databases of high interest for the quantification of exposure-risks relationships. In addition to what has already been done in the frame of the Alpha-Risk project, many additional pertinent analyses could be developed on this basis in the future, especially regarding the quantification of risks associated to low dose rate chronic exposures, the impact of internal contaminations, the estimation of radiation quality, and the evaluation of radiation induced non cancer effects.

There are a series of questions that need further developments as well as routes of further research, i.e. improvement in organ doses calculation, specific analyses of

endpoints with small numbers of cases, collection of incidence data, risk analysis among women, non cancer issues, development of molecular epidemiology, identification of biomarkers, etc. These questions could be ideally addressed in a world-wide pooling of updated uranium miners studies and nuclear workers with higher statistical power. The European collaboration settled in the Alpha-Risk project could play an important role in the development of these further researches.

Some methods developed in the frame of the Alpha-Risk project could be exported to other populations. For example, the projection method developed by RIVM to project the smoking data from a case-control study to a cohort study may be adapted to be applied to other populations of miners and nuclear workers or in other frameworks. Also, the calculation of organ doses elaborated in collaboration between WP1 and WP5 should be extended to other populations of miners. A similar extension of organ dose calculation to nuclear workers populations was shown to be feasible within WP3 and WP4.

The work conducted in the frame of WP4 highlighted the feasibility and pertinence of developing a large joint cohort study of nuclear workers with internal exposure in France and in the UK, with a long term follow-up.

Comparison of results with those obtained in other populations with different types of exposure may also be of great interest in radiation protection in order to get more insight in the assessment of radiation quality factors. Combining different modelling approaches (classical statistical approaches and biologically-based models) would be necessary for such a comparison, and in this regard, the experience acquired in the Alpha-risk project could prove of great interest.

## **Conclusion**

This project involved three different fields of research: epidemiology, internal dosimetry, and mechanistic modelling. This collaboration allowed the exchange of data between different partners, and permitted fruitful discussions between researchers with different background and an internal critical assessment of the data quality, of the methodology and research protocols, and of the results. This tight collaboration was a necessary basis to succeed in synthesising the results obtained from both occupational and residential exposure data in regards to the most common alpha emitters, such as radon, uranium, plutonium and their decay products.

This project has led to a better knowledge of the effect of radon inhalation, and provides more information about factors that modify the associated lung cancer and leukaemia risk. The synthesis of the results of both residential and occupational radon exposure data represents the state-of-the-art knowledge on the effect of radon exposure at low doses and low dose rates. New light has been shed on the interaction between radon exposure and tobacco smoking in lung cancer initiation. This in turn should assist in the management of radon exposures and in formulating advices on lung cancer prevention. As a consequence, a net benefice to health is expected.

On the other hand, an important progress was achieved with respect to studying effects of protracted, low level exposure to uranium and plutonium isotopes. The lung cancer case-control study, with over 500 cases and their matched controls, has provided the first opportunity to estimate directly the relationship between Pu and U dose and the risk of lung cancer. Although statistical power to estimate the effect of internal exposure on the risk of leukemia is low at this stage, the common protocol of

data collection and analysis of the dose – response relationship was set up on the European level, both for case-control and cohort studies. Further continuation and follow-up of these studies, including additional lung cancer and leukemia deaths, and inclusion of cases and controls from other cohorts of Pu and U workers worldwide would be important in order to provide more precise direct estimates of the effect of these exposures.

The datasets implemented and improved during this project constitute a very good basis to quantify the risks associated with chronic exposures to internal radiation at relatively low dose rate. The size of the datasets, the long term follow-up and the quality of the exposure and dosimetry data ensure the capability to detect low risks, and to determine the impact of effect modifiers. Long term follow-up would allow the analysis of potential risk for non cancer causes of death. Furthermore, the work performed in the recent years has allowed the collection of data on other risk factors (tobacco smoking, diagnostic chest x-rays, and chemical exposures). These data will enable further multifactorial analysis of risk, and the consideration of the joint effects of concomitant exposures and more precise estimation of risk related to internally incorporated alpha emitters.