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α-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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Executive summary

Introduction

In radiation epidemiology many studies have been carried out on the effects of external photon exposure, based on the Japanese A-bomb survivors and on patients with medical exposures. 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 present project aimed to regroup major studies in Europe that are able to answer more precisely the questions of long-term health effects in relation to chronic internal exposure. 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: 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. Such a study is necessary to fill important gaps in current scientific knowledge and to assure a long term follow-up of these cohorts. 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.

WP5 - Organ dose: This WP aimed at calculating estimates of individual absorbed doses to specific target tissues (lung regions, red bone marrow (RBM), kidney, liver) and associated uncertainties in relation to characteristics of individuals (attained age, smoking habits). Doses estimated under this work package 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 work package 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^3) 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 (RBD) 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). RBD 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 dose reconstruction with the common dose reconstruction approach within WP3

- 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 in the WP3 case-control study.
- Elaboration of the common protocol to produce 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 from WP6 as a modified version of the BEIR VI Exposure-Age-Concentration model, fitted to the European miner case-control data below 300 WLM. 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. No adjustment was made for the effect of exposure rate, as the focus here was on application to low exposure rates. 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-EAC model gives the highest values. The lifetime risk estimates from the WP6 and WP1 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. The similar extension of organ dose calculation to nuclear workers populations was shown to be feasible within WP3 and WP4.

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.

Introduction

Radiation protection guidelines are mainly based on studies of populations exposed to external radiation. In radiation epidemiology much work has been carried out in the past on the effects of external photon exposures, based on the Japanese A-bomb survivors and patients with medical exposures. Today, one of the main issues in radiation protection is the long-term effects of exposure to other radiation types, like alpha-emitters that the general public inhales daily at low levels through domestic exposure and to which various subgroups of nuclear workers are exposed during occupational life.

In Europe, through previous research programmes (FP4: Tirmarche et al. 1999, FP5: Tirmarche et al. 2001), important progress have been achieved in studying effects of exposure to radon and its decay products. Basic data from epidemiological studies of uranium miners from the Czech Republic (Tomasek et al. 2003; Tomasek 2002), France (Laurier et al. 2004; Rogel et al. 2002) and Germany (Kreuzer et al. 2002), with individually registered and validated exposures to radon decay products have been put together and information on uranium dust and external gamma radiation has become available for a large sub-cohort. Joint risk estimates from the Czech and French cohorts based on a large population (10,000 individuals) have been provided. Moreover, the large German cohort of Wismut was also included in the previous contract. However, only descriptive results were available for this cohort at the end of our FP5 programme in September 2003. The main methodological issues of these epidemiological studies are the quantification of potential health risks at various levels of exposure, and how the dose-response relationship varies with factors such as attained age, time since exposure, age at exposure, and exposure rate.

Parallel to the joint analysis of data from the miners' studies, a European effort has taken place to analyse jointly individual data from large case-control studies on lung cancer and indoor radon exposure (Darby and Hill, 2003). However the estimation of the numbers of radon-induced lung cancers occurring following exposures at different radon concentrations needs further methodological improvements, for instance by taking into account specific characteristics of the populations concerned (on a national level, or on a regional level if the study is focused on a specific radon prone area) or by taking experience of the various indicators (age, sex, smoking, socio-economic class, education) studied under the common European protocol concerning the case-control studies. Synergy between radon exposure and tobacco smoking is another important concern for the formulation of appropriate public health policies.

In regards to the long-term effects in populations exposed to plutonium (Pu) and uranium (U) isotopes only little information was available. Studies of workers in the nuclear industry have up to now mainly focused on the health effects of exposure to external photon radiation (Cardis et al 1995). However, workers employed in some facilities – particularly facilities involved in the fuel cycle – are potentially exposed not only to photons, but also to a number of radionuclides such as uranium and plutonium, which enter the body by inhalation, ingestion or through accidents resulting in percutaneous wounds. A major target for these nuclides, following inhalation, is the lung. Internal deposition of uranium isotopes also results in doses to the lymphatic system, while plutonium is also deposited in the liver and bone surface. The quantification of risks associated with exposure to U and Pu isotopes is therefore of particular public health and radiation protection concern.

The project “Alpha Risk” aimed to regroup major studies in Europe in order to answer more precisely the questions of long-term health effects in relation to chronic internal exposure to alpha emitters such as radon, uranium, and plutonium.

The project was based on collaboration between epidemiologists, statisticians, occupational physicians and experts in dosimetry. This tight collaboration gave the opportunity *i)* to estimate excess risk coefficients per organ dose in relation to time-dependent variables, *ii)* to take into account co-factors like occupational chemicals, tobacco, gender, age at exposure and attained age, *iii)* to assess uncertainties linked to exposure estimates and introduce them into dose-risk models, and *iiii)* to calculate specific risk factors per organ dose instead of per units characterising environmental measurements (for example, Working Level Month (WLM) or Becquerel (Bq) per m^3 .

The project constituted an extension of researches initiated in the previous European Frame Projects. It consisted of 7 work-packages. Figure 1 summarises the organisation of the project into work-package.

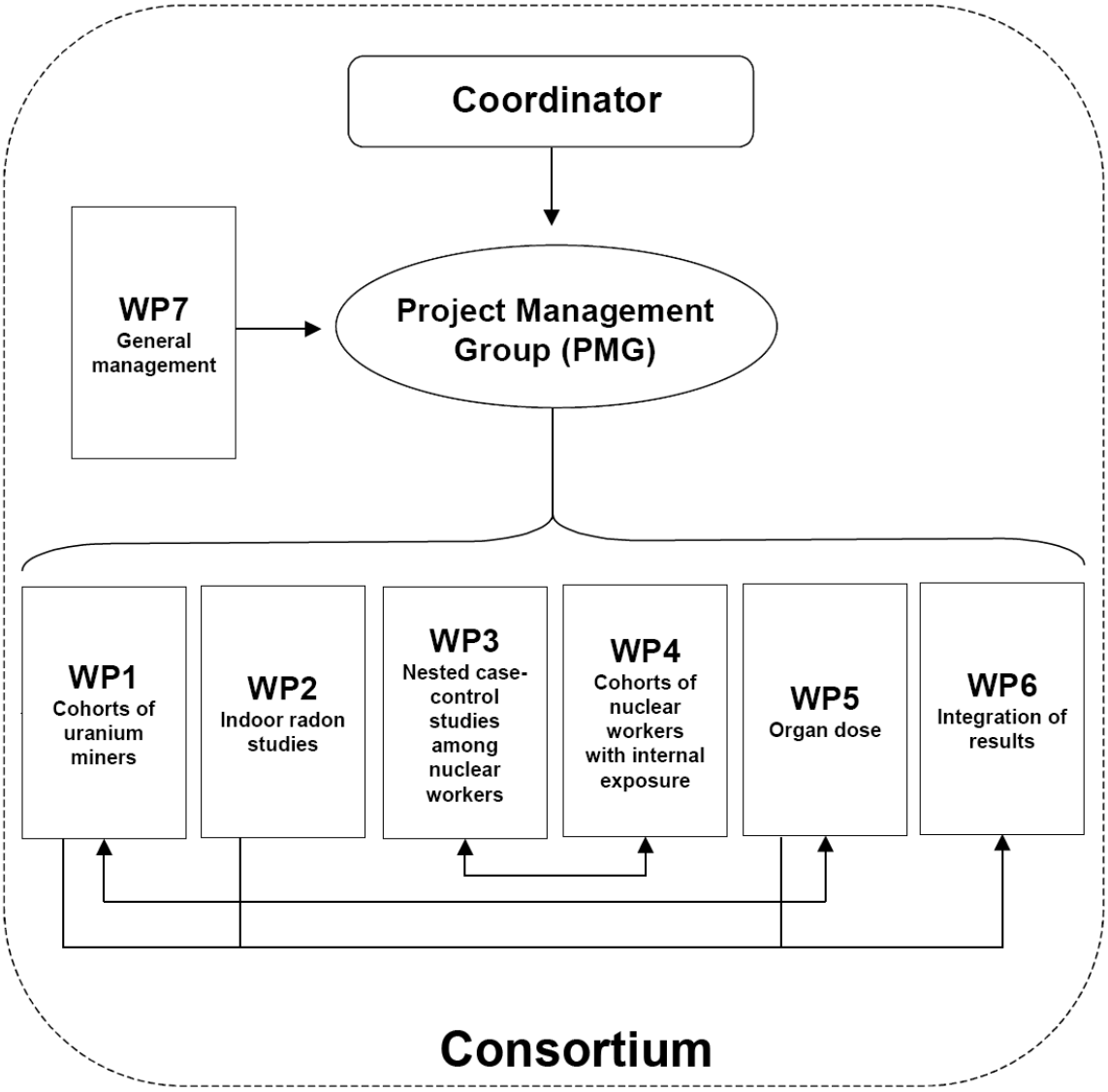

Fig. 1: *Organisation of the project into work-packages (WP)*

Work-package 1 aimed at quantifying cancer (lung cancer, leukaemia, kidney cancer, etc.) and non-cancer risks associated with radon exposure, combined or not with other pollutants in mines or with tobacco exposure, using advanced statistical methodology.

Work-package 2 aimed to describe the different factors able to influence exposure characteristics in those countries involved in the joint European analysis and make a synthesis defining the most appropriate data for a risk assessment approach.

Work-package 3 aimed to derive lung cancer and leukaemia mortality risk estimates for exposure to specific radionuclides (uranium and plutonium) in nuclear workers in Europe through a nested case-control study, and to estimate the joint effects of internal and external radiation.

Work-package 4 aimed to determine the feasibility of a joint statistical analysis of the cancer and non-cancer mortality experience of the French nuclear industry and UK-BNFL plutonium and uranium worker cohorts.

Work-package 5 aimed to calculate estimates of individual organ doses and associated uncertainties in relation to exposure and to individual characteristics (i.e. attained age, smoking habits, etc.) for the epidemiological studies included in WP 1, to quantify all uncertainties affecting these doses, and to select the “best” models by comparing different modelling approaches.

Work-package 6 aimed to integrate findings from other work packages, with a particular focus on radon, so as to arrive at overall cancer risk estimates for different exposure scenarios from studies of occupational and residential radon exposure.

In addition to these scientific work-packages the seventh work-package was devoted to the scientific and technical coordination and general management of the project.

This final scientific report presents the scientific achievements for the whole period of the contract, from July 2005 through October 2009. The material, methods, results, and production are presented by work package.

Work package 1: Cohorts of uranium miners

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1.1 Context and work package objectives

Uranium miners constitute a population that is directly relevant to the analysis of long term detrimental health risks associated with exposure to alpha emitters. Several studies have been launched in different parts of the world since the 60's, and research on this topic has been supported in Europe by the EC for many years (FP4 contract FI4–CT95–0031 1996–99, FP5 project FIGH-CT1999–00013 2000–2003).

The activity of the Alpha-Risk project Work-Package 1 (WP1) constitutes the direct continuation of these previous studies within the Framework Programme 6. WP1 aimed at the development of studies of uranium miners in Europe, toward a better quantification of the risks associated with internal and external radiation exposure at low levels of exposure. The specific objectives are detailed below:

- Developing large sized cohort studies in Europe with a precise reconstruction of multiple professional exposures (radon, gamma rays, ore dust). The project included three cohorts in France, Germany and the Czech Republic, with long term follow-up. The construction of a joint cohort, combining data from these three cohorts, provided the basis for a powerful analysis of the risks, not just limited to lung cancer mortality, but also to leukaemia, kidney cancer and non-cancer mortality (especially cardiovascular diseases);
- Investigating the joint effects of smoking and radon exposure on lung cancer risk by carrying out case-control studies nested within the three cohorts. A leukaemia case-control study was also conducted on the basis of the German WISMUT Health Archives. Results were compared with those from the cohorts;
- Quantifying risks among miners using organ doses to the lung, red bone marrow, kidney and liver. The organ doses calculations were carried out in close co-operation between the epidemiologists of WP1 and the dosimetrists of Work-Package 5 (WP5). These scientists were able to exchange experience regarding the working conditions in uranium mines, the uncertainties associated with miners' exposures, the amount of available data and the characteristics of the dosimetric models;
- Statistical modelling of the dose-response relationship involving factors such as time since exposure, age at exposure and dose rate. Elaborated statistical methods were applied in modelling the dose-response relationship. Measurement errors in radon exposure were characterized for the three cohorts and the impact of these uncertainties on the radon associated lung cancer risk (estimated through a biologically based model) was analysed. A method was proposed for the extrapolation of smoking information, only available for a subset of the cohort, to an entire cohort. The lung cancer risk associated with radon exposure and smoking was analyzed using a two-mutation carcinogenesis model with clonal expansion. The floating absolute risk methodology was also applied to case-control data from WP1.

To achieve these different objectives, WP1 involved researchers from seven different organisations in Europe. It relied on a multidisciplinary collaboration between epidemiologists, statisticians, mathematical modellers and dosimetrists. A tight collaboration was developed with dosimetrists from WP5 for the estimation of risks among miners based on the calculation of organ doses. In total, twelve meetings were organised within the framework of WP1, among which seven were joint meetings with WP5.

1.2 Scientific results

1.2.1 European cohort of uranium miners

The first aim of the project was to describe the characteristics of the three cohorts of uranium miners, and to fix the conditions for the completion of a joint European database. Completion of this aim involved essentially the three partners involved in the management of the cohorts: IRSN for the French cohort, BfS for the German cohort and NRPI for the Czech cohort. This step proved more complicated than initially scheduled, and a large amount of work has been done to collect additional information, to fix standardized formats for data exchange between partners, and to characterize the data in a similar way. Table 1.1 presents the main characteristics of the three cohorts and of the resulting European combined cohort.

Table WP1.1*. Population size and follow-up for the three cohorts of uranium miners, separately and combined*

	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
Vital status n (%)				
lost to follow-up	66 (1)	393 (4)	1,113 (3)	1,572 (3)
dead	1,467 (29)	3,947 (39)	4,519 (13)	9,933 (20)
alive at end of study	3,492 (69)	5,577 (56)	29,336 (84)	38,405 (76)
age > 85	61 (1)	62 (1)	116 (0)	239 (1)
Mean (min-max) in years				
length of follow-up	30.1 (>0–53)	26.3 (>0-48)	25.9 (>0–43)	26.4 (>0–53)
age at entry in study	28.8 (16–68)	30.2 (17-68)	22.7 (13–66)	24.8 (13–68)
age at end of study	58.9 (20–85)	56.6 (19-85)	48.6 (15–85)	51.2 (15–85)
Mortality				
all causes	1,467	3,947	4,519	9,933
all cancers	544	1,510	1,179	3,233
lung cancer	159	922	462	1,543
kidney cancer	20	38	36	94
leukaemia	15	31	35	81

The European cohort finally includes more than 50,000 male miners with a long duration of follow-up and individually reconstructed exposures to both radon and radon decay products, long lived radioactive ore dust and external gamma rays. Close to 10,000 deaths were recorded, including more than 1500 lung cancer deaths. This very large population provides the basis for an analysis with a high statistical power of long term health effects of exposure to alpha emitters. The low percentage of individuals lost to follow-up indicates the very good quality of the cohorts.

The general conditions in the mines have been reconstructed in the three countries for different periods, regarding ventilation, methods of uranium extraction, mechanisation, etc. The exposures to radon, external gamma rays and long lived uranium dust have been described (Table 1.2). Compared to most studies from the literature, the levels of exposure to radon were rather low, protracted over a long duration of exposure. The quality of exposure assessment methods has been evaluated using the same criteria in the three countries. For

radon exposure, it appeared that exposure assessment was of good quality for the periods from 1956 in the French cohort, 1953 in the Czech cohort and 1956 for the German cohort. This work provides the basis for analyses of the risk among miners with low levels of exposure rate and good quality of exposure assessment over a large population.

***Table WP1.2**. Description of employment and of the three radiological exposures in the three cohorts separately and combined*

	France	**Czech Republic**	**Germany**	**Total**
Employment period	1946–1989	1937–1974	1955–1989	1937–1989
Duration of employment (y)*	16.4 (1.0–54.0)	6.9 (0.6–36.6)	11.8 (0.5, 40.0)	10.9 (0.5–54.0)
Cumulative exposure among exposed miners				
Radon (WLM)*	36.6 (0.03–960.1)	72.8 (0.1–869.8)	55.9 (>0–1252.8)	58.0 (0.03–1253)
External gamma (mSv)*	54.7** (0.2–470.1)	45.6 (0.7–276.5)	33.5 (>0–616.2)	38.0 (>0–616.2)
Long lived radionuclides (kBq.m-3.h)*	1.6** (>0–10.0)	12.1 (0.2–70.3)	1.6 (>0–68.5)	4.1 (>0–70.3)

* : mean (min-max) ** : available only after 1956 in the French cohort, WLM: working level month

Mortality risk in the three cohorts and in the European joint cohort has been analysed by comparing the observed numbers of death with those expected from national mortality rates. An excess of lung cancer death was observed in each of the three studies. The estimated standardized mortality ratio (SMR) in the joint cohort was SMR=2.27, with 95% confidence interval (CI)=[2.16–2.38]. Apart from lung cancer, no excess of death from other types of cancer was observed in the joint cohort. However, in some of the three cohorts excesses for specific cancer types were noted. In the Czech cohort, the mortality for all causes of death and the mortality for most cancer sites were significantly elevated, but it should be noted that, in comparison to the other two cohorts, the estimated SMR was generally higher. An elevated risk of leukaemia was observed in the Czech cohort: SMR=1.53, with 95%-CI=[1.04–2.17]. An elevated risk of kidney cancer mortality was observed in the French cohort (SMR=2.00, 95%-CI=[1.22–3.09]) and in the Czech cohort (SMR=1.41, 95%-CI=[1.00–1.93]). Mortality risks were published in each of the three counties (Tomasek et al, 2006; Grosche et al. 2006; Vacquier et al. 2008).

For causes of death other than cancer, a global excess was also observed in the Czech cohort (SMR=1.22, 95%-CI=[1.17–1.26]), but not in the two other cohorts nor in the joint cohort. No excess of mortality for cardiovascular diseases was noted in the whole German cohort (1946-1998)(Kreuzer et al. 2006) nor in the French cohort (Nusinovici et al. submitted), but an exposure-risk relationship was noted in the French cohort between cerebrovascular risk and cumulative radon exposure (Nusinovici et al. submitted).

1.2.2 Modelling of the relationship between radon exposure and lung cancer risk

Epidemiological evaluation of lung cancer risk among uranium miners has been conducted since the late 1960s. The risk was consistently found to depend linearly on cumulated exposure to radon progeny. The magnitude of risk estimates, however, differed. More recent studies aimed at evaluation of modifying factors such as time since exposure, attained age, exposure rate, age at exposure or quality of exposure (Tomasek et al. 2008). The aim of Deliverable D1.4 was to verify these modifying effects and to estimate the risk from low exposure at low exposure rates, which are also characterized by good quality of exposure estimates. These analyses were realized on the basis of the Joint European cohort of uranium miners constructed within the framework of WP1, where a large proportion of

exposure is based on extensive measurements and personal monitoring. This work was conducted by NRPI, in collaboration with IRSN and BfS.

Analyses considered the radon exposure cumulated over the whole occupational history of each miner individually. Large variations occurred in time, which were related to the method of uranium extraction, the conditions in the mines, the levels of exposure, and the quality of exposure assessment. Broadly, the first periods in each study are characterized by higher mean exposure levels and lower quality of exposure estimates and the latter periods are characterized by low mean levels of exposure and good quality of exposure estimates. This is illustrated in Figure 1.1.

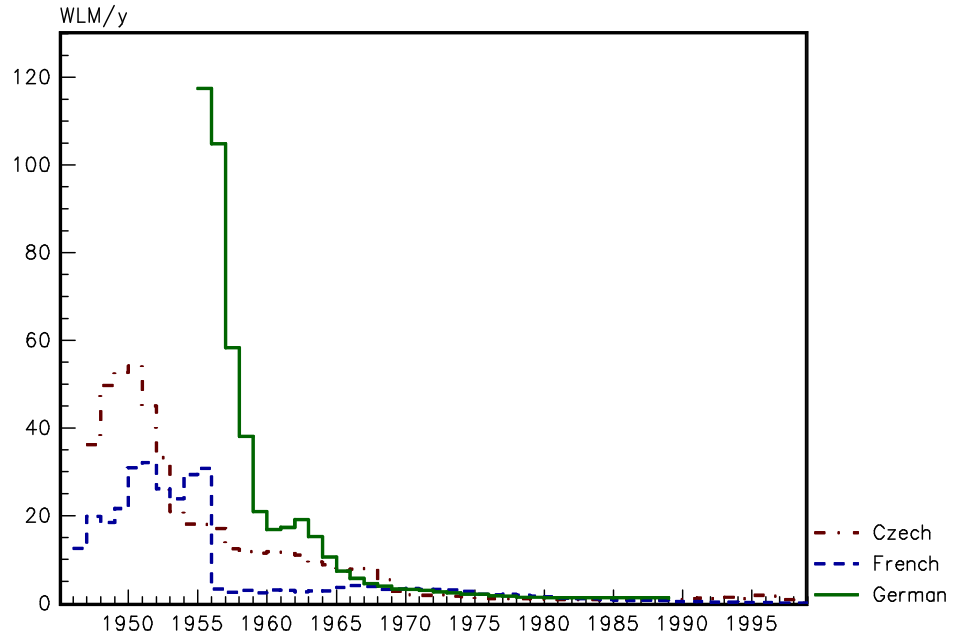

Fig. WP1.1. *Mean annual radon exposures in the three European cohorts of uranium miners*

All exposure-risk analyses were conducted by internal Poisson regression using linear excess relative risk (ERR) models. The overall ERR per 100 WLM estimates in the three cohorts appear substantially different, with a higher estimate obtained in the Czech cohort compared to the two other cohorts (Table 1.3, left part). Nevertheless, considering only exposure windows with good exposure quality and low exposure rates (since 1953, 1956 and 1967, respectively in the Czech, French and German cohort, Table 1.3, right part), the estimated ERR per 100 WLM were much closer and the heterogeneity between the three countries was no longer significant. The resulting exposure-lung cancer risk coefficient in the European combined cohort was ERR = 2.60 per 100 WLM, (95%-CI= [1.83–3.36]). The differences in the estimated ERR/WLM between whole cohorts and period-restricted subsets could reflect the effects of several concomitant factors: better quality of exposure assessment in the later periods, lower exposure rates and shorter time since exposure. Indeed, no substantial differences were seen in the estimated exposure-risk relationship between the three cohorts when temporal and exposure period modifying factors were included in models.

Table WP1.3. *Global and period of exposure specific estimates of the excess relative risk (ERR) of lung cancer per 100 working level months (WLM) in the Czech, French, and German cohorts without consideration of time modifying factors*

	Whole cohorts		**Low exposure rate period ***	
Cohort	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, using a modified external background rate estimation method.
* Exposures since 1953, 1956 and 1967, respectively in the Czech, French and German cohort

In 1999, detailed analyses of the exposure risk relationship were performed in the BEIR VI report, which lead to a preferred model taking into account windows of exposure defined according to time since exposure (TSE), and modifying factors for categories of attained age and exposure rate (C°) (NRC 1999). All modifying fa ctors identified in the BEIR VI report (NRC 1999), particularly the effects of time since exposure, attained age, and exposure rate, were found to be similar in the present analyses. A model similar to the one proposed by the BEIR VI report has been developed (denoted as the BEIR VI like model). In addition, we conducted analyses based on simultaneous exposure windows based on time since exposure, age at exposure (AE), and exposure rate, which are principally more appropriate in studies of chronic exposure. Therefore, this model was preferred to the other models in the Alpha-Risk project. The projection of the ERR estimated from these three models using the same scenario of exposure is illustrated in Figure 1.2. The estimated ERR appears very similar in all models, indicating that the different approaches are very coherent in regard to the evaluation of the effect of the exposure-risk modifiers.

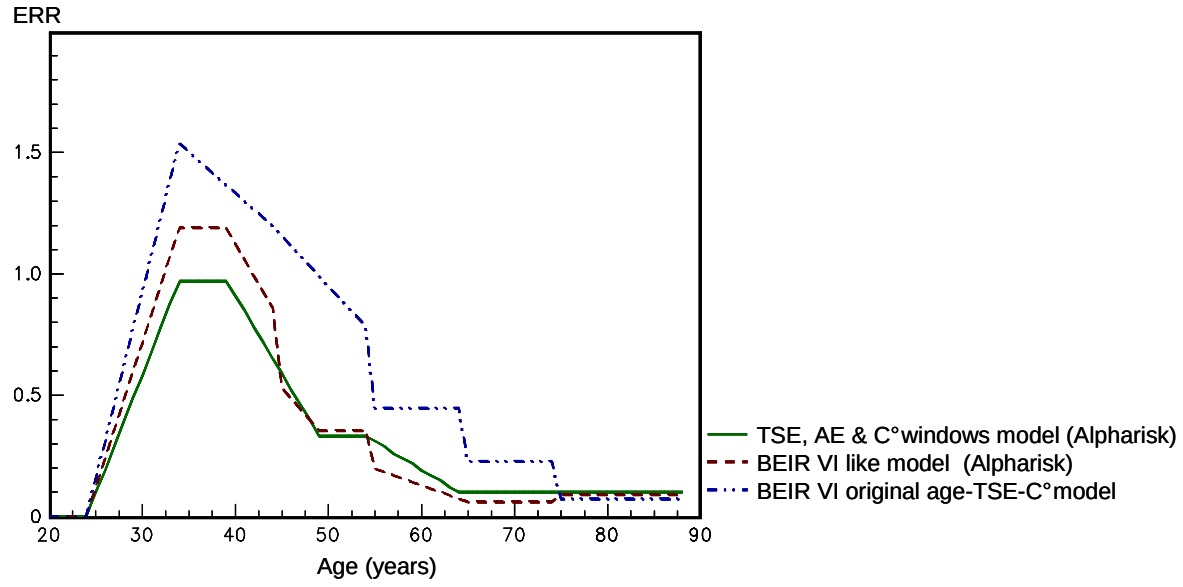

Fig. WP1.2. *Projection of the excess relative risk (ERR) estimated using three different models for an individual exposed to 2 WLM per year from age 20 to 29 (see text for explanation of the 3 models)*

1.2.3. Analysis of the joint effect of tobacco and radon exposure on lung cancer risk in nested case-control studies

A major limitation of the French, German and Czech uranium miners' cohorts is the lack of individual smoking information, an important risk factor for lung cancer that may confound or modify the estimated relation between radon and lung cancer risk. In the EC 5th Framework Program, three case-control studies nested within the French, German and Czech cohorts had been set out in order to assess the joint effects of radon exposure and smoking on lung cancer death risk among uranium miners. In the framework of the Alpha-Risk project, these nested case-control studies were completed, the exposure-risk relation between radon and lung cancer death adjusted for smoking was estimated separately in the three studies (Deliverables D1.2 and 1.5), and the feasibility of a pooled analysis of the three datasets was examined. Deliverable D1.2 provides a detailed description of the French, German and Czech case-control studies. At the time when this deliverable was submitted, the collection of the Czech smoking data was not finished. Deliverable D1.5 presents an updated description of the three studies, the collection of smoking data having been completed for the three countries, and the results of the analysis of the joint effects of radon exposure and smoking on lung cancer death risk in the three individual nested case-control studies.

The nested case-control approach relies on the analysis of a subset of individuals selected from the cohort: the cases (miners deceased from lung cancer) and the controls (miners of the same cohort, with similar characteristics for age, period of birth… but free of lung cancer). Missing information, smoking information in this case, is collected retrospectively. This procedure allows the estimation of relative risks and interactions between risk factors whereas data collection can be focused on a much smaller subset than the complete cohort.

The study design in each country was adapted to the available sources of data. Administrative and occupational information was available for all miners from the respective cohorts. Sources of smoking information consisted in occupational medical files and individual questionnaires. Table 1.4 displays the number of cases and controls with available smoking information for the three studies. Altogether, the population consists of 1155 cases and 2431 controls.

Table WP1.4*. Summary of the availability of smoking information in the three studies*

	French study		**Czech study**		**German study**	
	Cases	Controls	Cases	Controls	Cases	Controls
Targeted population	100	500	672	1491	704	1398
Individually matched sample with smoking information appropriate for analyses	62	320	672	1491	421	620
Percentage reached	62%	64%	100%	100%	60%	44%

For the French study, the percentage of ever smokers is 90% among cases and 73% among controls. The crude relative risk (RR) of lung cancer death associated with being an ex-smoker relative to the reference level of never-smokers was equal to 3.32 (95%-CI: 1.32–8.35). Fitting a linear ERR model for cumulative radon exposure yielded an ERR/WLM equal to 0.98% (95%-CI: 0.18 –3.08%). Temporal modifying effects of attained age, time since first exposure, time since last exposure and period of exposure were investigated. The ERR/WLM tended to decrease as attained age increased. When a multiplicative model was fitted for radon exposure and smoking status, the estimated ERR/WLM was 0.85% (95%-CI: 0.12–2.79%) and the estimated RR for smoking was equal to 3.04 (95%-CI: 1.20–7.70). A likelihood ratio test between the model including only smoking status and the model containing smoking status and cumulative radon exposure was statistically significant

(p=0.008), as was that comparing the model with only CRE and the model containing CRE and smoking (p=0.010).

For the Czech study, the percentage of ever smokers is 92% among cases and 73% among controls. The crude RRs of lung cancer death were equal to 1.82 (95%-CI: 1.29–2.56) for ex-smokers ≥ 10 years and 6.36 (95%-CI: 4.79–8.45) for other smokers relative to the reference level of never-smokers. Fitting a linear ERR model for cumulative radon exposure yielded an ERR/WLM equal to 1.96% (95%-CI: 1.07–3.98%). When a multiplicative model was fitted for cumulative radon exposure and smoking status, the estimated ERR/WLM was 1.54% (95%-CI: 0.79–3.37%) and the estimated RRs for smoking were equal to 1.82 (95%-CI: 1.28–2.59) for ex-smokers ≥ 10 years and 6.03 (95%-CI: 4.51–8.07) for other smokers. ERRs by smoking status categories were calculated and more detailed analyses investigating effects of quantities smoked were also provided for the Czech study.

For the German study, the percentage of smokers (current smokers and ex-smokers for less than 20 years) is 95% among cases and 75% among controls. The crude RR of lung cancer death for smokers compared to non-smokers (defined as never-smokers and ex-smokers more than 20 years) was 7.61 (95%-CI: 4.43–13.07). Fitting a linear ERR model gave an estimated ERR/WLM associated to radon exposure equal to 0.25% (95%-CI: 0.13–0.46%). Possible modification by temporal factors of the exposure-response relation between the risk of lung cancer death and radon exposure was investigated. Time since last exposure had a significant decreasing effect on risk and the modifying effect of attained age was nearly significant. When a multiplicative model was fitted for radon exposure and smoking status, the estimated ERR/WLM was 0.23% (95%-CI: 0.11–0.46%) and the estimated RR for smoking was equal to 7.45 (95%-CI: 4.27–13.01).

In the framework of the Alpha-Risk project, a feasibility study regarding the joint analysis of the data of the three studies was planned. A common format for the three databases has been adopted. Eventually, the analysis of the pooled data was ruled out before the end of the project. Analyses were performed on 1046 cases and 2492 controls. The results showed a significant effect of radon exposure on lung cancer risk after adjustment on smoking status. Adjustment on smoking decreased the risk coefficient associated to radon very slightly. The results were compatible with a sub multiplicative interaction between radon exposure and smoking. ERRs estimated by categories of smoking status are displayed in Figure 1.3. The results of this large case-control miners study will be the subject of a future scientific publication.

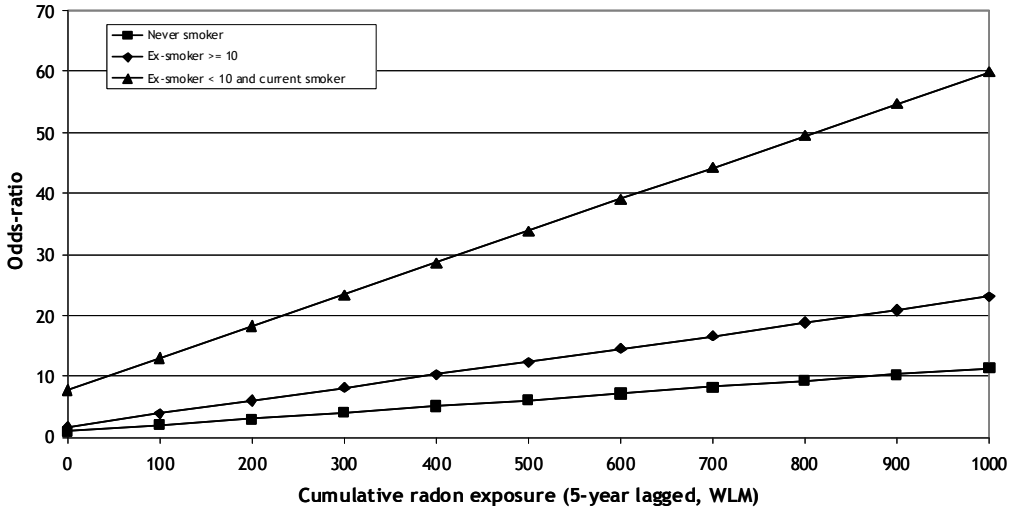

***Fig. WP1.3**. Risk of lung cancer death associated with cumulative radon exposure by smoking categories in the pooled European miners study.*

The work carried out during the Alpha-Risk project has allowed the reconstruction of smoking information for part of the miners of the French, Czech and German cohorts. The availability of smoking information made it possible to analyse the risk of lung cancer death related to cumulative radon exposure taking smoking into account. For each of the three nested case-control studies, the radon risk estimates did not differ much with and without adjustment for smoking. Risk estimates related to radon exposure were in agreement with the estimates derived from the corresponding cohort study. Thus smoking seems no major confounder for the cohort studies. Moreover, a pooled analysis was performed on the largest miner case-control sample in Europe and confirmed the conclusions drawn from the BEIR VI analyses and the indoor radon pooling European study.

1.2.4. Analysis of case-control miner data using the floating absolute risk methodology

In epidemiological studies, it is common to present relative risks with respect to a baseline exposure level. However, in such calculations, the risk of the baseline level is set as one and it does not have any standard error associated with it. If this baseline category contains little data, the confidence intervals can be highly inflated for risks of non-baseline categories, and any risk difference between non-baseline categories may be obscured. The floating absolute risk (FAR) is an alternative way of presenting relative risk estimates for categorical risk factors. This method involves calculating confidence intervals of risks for non-baseline categories without the influence of the baseline category. It assists in the graphical presentation and interpretation of results.

In the framework of the Alpha-Risk project, the FAR methodology was applied to the results of the lung cancer nested cases-control studies developed in Work-Package 1. Calculations were applied to the categorical analyses of the combined dataset. The work was conducted by HPA, in collaboration with the teams in charge of the three nested case-control studies (IRSN, BfS, NRPI).

We estimated the odds ratio (essentially equivalent to the relative risk) of lung cancer death for different categories of cumulated radon exposure truncated at the index year lagged by 5 years, with the reference category being 0 WLM and adjustment made for smoking status. In the standard analyses without FAR, the confidence limits for the odds ratio are wide because the confidence intervals for non-baseline categories contain a common component of variance due to random variation in the risk for the baseline category (Figure 1.4a).

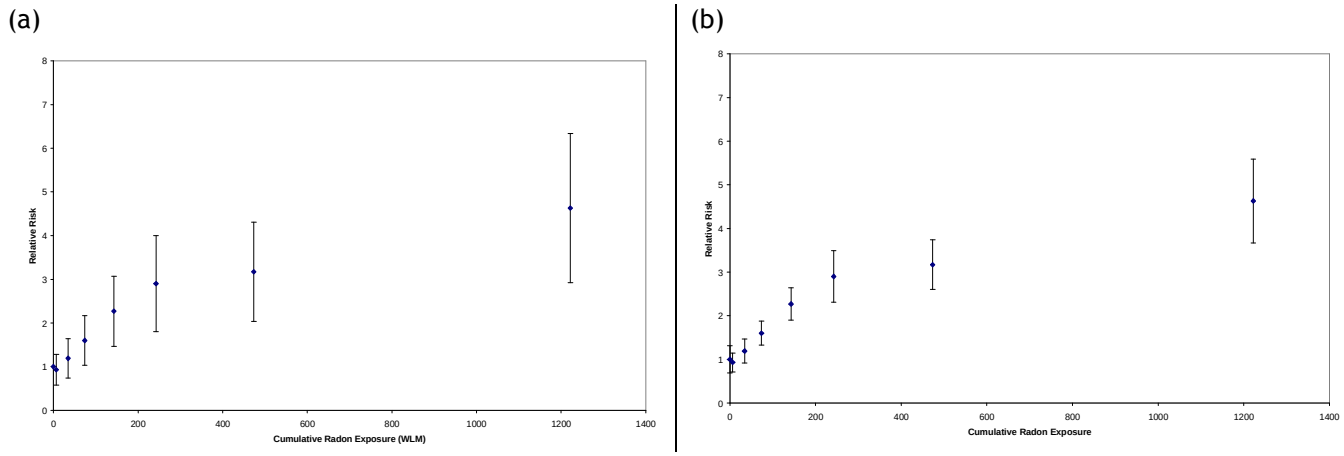

Fig. WP1.4. *Odds ratio of lung cancer death adjusted for smoking status for categories of cumulative radon exposure, without (a) and with application of the FAR method (b).*

Using the FAR method, the confidence limits for non-baseline categories are reduced considerably because the random error associated with the baseline category is restored to the baseline (Figure 1.4b).

Floating absolute risks provide a means of improving the uncertainty estimates for relative risks for categorical risk factors. They allow confidence intervals of risks for non-baseline categories to be calculated without the influence of the random variation in the baseline category. This method assists in the graphical presentation and interpretation of results from case-control analyses, specifically for uranium miners data.

1.2.5. Use of nested case-control data on smoking and analysis of lung cancer risk with biologically based models, including separate description of the effects of tobacco and radon exposure histories

The objective of this work was to quantify, from European miners data, the lung-cancer risk that is related to the exposure to radon and smoking behaviour using the two-mutation carcinogenesis model (TMC) with clonal expansion. This work was conducted by RIVM, in collaboration with the researchers in charge of the German cohort (BfS).

As cohort-wide information on smoking habits is very limited, a new technique (the Monte-Carlo L_δ-projection method) was developed to overcome this problem by using information on the tobacco consumption from case-control studies (CCS) nested within these cohorts (Deliverable D1.6). All procedures developed in D1.6 were visualized using a German CCS of WISMUT miners, but are equally well suited for application to other CCS studies nested in miner cohorts.

Assuming that the smoking habits of uranium miners included in a CCS are characteristic for the smoking habits of miners in the entire cohort population, the technique used a pseudo-random mapping routine projecting smoking parameters (e.g. start age, number of cigarettes per day, duration) onto the cohort database, constrained by the corresponding distributions in the CCS. The randomly assigned smoking habits then served as a proxy for the actual, unknown smoking habits of each miner. Several smoking parameters could then be mapped directly onto the cohort.

However, as several of these parameters might be correlated, the concept of a *smoking-status* (L_δ-) *spectrum* in which these correlations were embodied was introduced. The spectrum was constructed by first dividing each smoking parameter into several bins. For each CCS-member it was then determined to which bins its parameters belong. A unique combination of bins was identified by an integer value *l*. The L_δ-spectrum was simply the fraction of miners that occupied smoking state *l*. It contained non-smokers, ex-smokers and current smokers, but was assembled from the CCS data for non-cases (L_0) and cases (L_1) separately. Figure 15 shows an example of a spectrum for non-cases consisting of 13 smoking states (black bars). Next, this Monte-Carlo technique was successfully applied to map the spectrum and the corresponding average parameter values onto the cohort. This is shown in figure 1.5 by the gray bars (projection onto 20,000 non-cases).

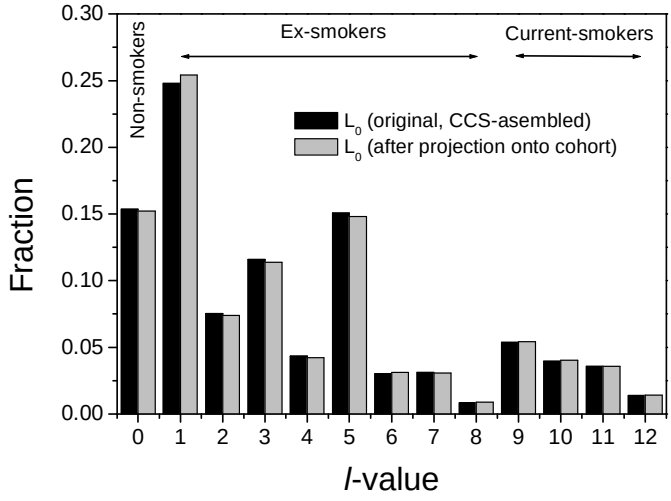

***Fig. WP1.5**. Illustration of the mapping method on a spectrum for non-cases consisting of 13 smoking states*

Deliverable D1.10 presents the analysis of updated miner studies with the biologically-based, two-mutation carcinogenesis (TMC) model, with a separate description of the effects of tobacco and radon-exposure histories. As detailed information on the tobacco consumption within the European cohort populations is missing, RIVM applied the so-called Monte-Carlo L_δ-projection outlined in deliverable D1.6. The analysis focused on the Alpha-Risk sub cohort of uranium miners employed at the WISMUT Company from 1946 to 1989 in the former German Democratic Republic.

First, the TMC model was applied to the German cohort data without explicitly accounting for the smoking behaviour. The model's free parameter values, found by using a maximum-likelihood technique, were similar to those found for the French uranium-miner cohort in a previous study (Brugmans et al, Radiat Environ Biophys 2004). Moreover, the TMC-expected lung-cancer mortality exhibits good agreement with the observed, age-dependent mortality.

Next, two smoking-status spectra were constructed from the German CCS: a spectrum for non-cases L_0 and one for cases L_1. They were (randomly) projected onto the cohort database, after which the assigned smoking habits were finalized by matching the age-related parameters with the attained age of the cohort members. A total of 256 independent L_δ-projections were carried out, each one followed by a TMC analysis of the resulting cohort file with proxy smoking data.

From the ensemble of calculations, a 'frequency-density' histogram was determined for each free TMC-model parameter. As an example, Figure 1.6 shows the distributions of the model's baseline parameters and the smoking related parameters, normalized with their respective ensemble-averaged values. This technique did not yield a single value for each parameter, but resulted in the probability of a parameter value lying in a certain interval. The resulting distributions showed that these parameters did not vary much more than a factor ~2 from their respective mean values, indicating that they were rather well determined.

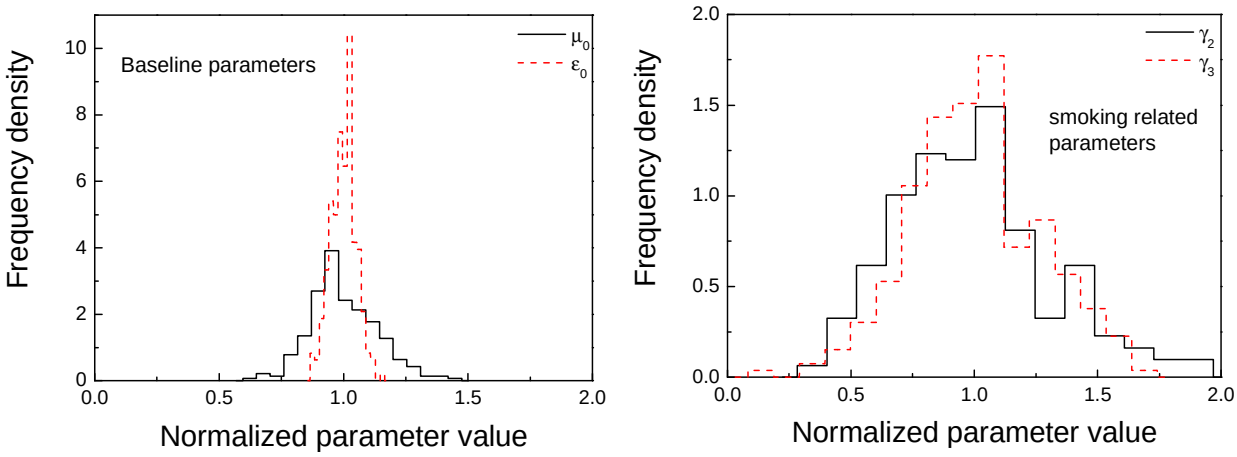

Fig. WP1.6*. Distribution of the two-mutation carcinogenesis (TMC) model's baseline parameters and smoking related parameters*

It was verified that the ensemble-averaged values did not change significantly by increasing the number of smoking states in the L_δ-spectra (i.e., *convergence* with respect to the L_δ-spectra). In conclusion, the proposed Monte-Carlo L_δ-projection appears to be suitable technique to account for the smoking behaviour of the miner population with well-determined distributions of the TMC-model parameters.

1.2.6. Characterization of exposure uncertainties and analysis of their impact on the radon associated lung cancer risk estimated through biologically based models

The work conducted by HMGU in the framework of WP1 had two aims; first to characterize radon exposure uncertainties in the European miner cohorts, and second to analyse the impact of these uncertainties on the radon associated lung cancer risk estimated through a biologically based model. This work was conducted in collaboration with researchers involved in the three cohorts (IRSN, BfS and NRPI).

Deliverable 1.7 presents models for radon exposure uncertainty for the European miner studies from the Czech Republic, France, and Germany in Alpha-Risk. The aim of the deliverable is to allow an estimate of the distribution of true exposures for each year of employment and each miner, for the given recorded exposures. In each of the three studies, several periods are identified which differ in the method or accuracy of exposure estimates, with reduced exposures and increased accuracy over time. When exposures are reconstructed e.g. from ambient measurements, the random errors are judged to be mostly of Berkson type (true exposures fluctuate around the recorded ones). In the later years in the French and Czech studies, the exposures are based on individual measurements. Then the classical error model (recorded exposures fluctuate around the true ones) is judged to be more applicable. In that case, the distribution of recorded exposures for given true ones is estimated in the deliverable. The inversion to an estimate of true exposures for given recorded ones requires the Bayes rule, and therefore the distribution of true exposures. In earlier studies, this was estimated from the distribution of recorded exposures, and the

above-mentioned conditional distribution. Therefore it was not included in this deliverable (but in deliverable D1.12, discussed below).

For the various conditional distributions, a log-normal form is used in such a way that the mean coincides with the recorded exposure. In this way the expected collective exposure does not change. Then the distribution is described fully by the width, for which the usual parameter sigma of log-normal distributions is used. It is tabulated in the deliverable for each of the different periods in the three studies. Figure 1.7 presents the distributions for exposure uncertainty in the French cohort after 1956.

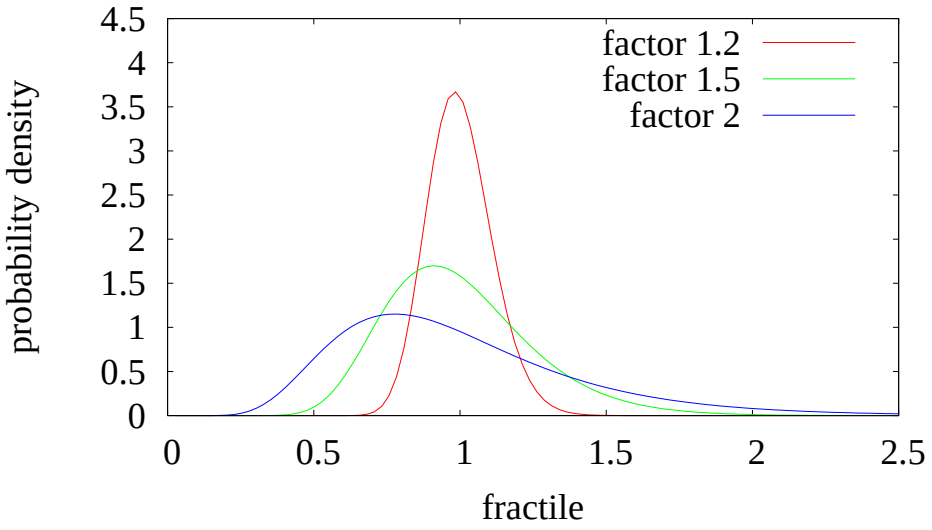

***Fig. WP1.7**. Probability densities proposed for different factors of measurement errors for the French cohort*

In addition there are special provisions in each of the three studies:

- In the Czech study, the exposure estimates of the hewers are judged to be more accurate than for other miners, which are reflected by more narrow distributions.
- In the French study, for the early years up to 1955 a systematic overestimation of recorded exposures is allowed, which is described with a combination of a triangular and a square distribution.
- In the German study, a job-exposure matrix is used for each year. Therefore in addition to the random uncorrelated Berkson errors, a correlated Berkson error for each year of exposure is included.

In deliverable 1.12 the biologically based two stage clonal expansion (TSCE) model is used to analyze lung cancer mortality in the European miner studies in Alpha-Risk. In all cases an action of radiation on initiation and promotion is allowed. All three studies indicate a highly significant action of radon on promotion. The action on initiation is not significant in the French cohort. An action on transformation was tested but not found to be significant. The model can describe all the data sets adequately, with different model parameters. The observed patterns in exposure, time since beginning of exposure, birth year, age and calendar year are reproduced well. The action of exposure rate on promotion is quite different in the French and German data sets on one side, and the Czech one on the other side. Figure 1.8 presents the estimated relative risks obtained using each of the three models on the basis of a low exposure rate scenario.

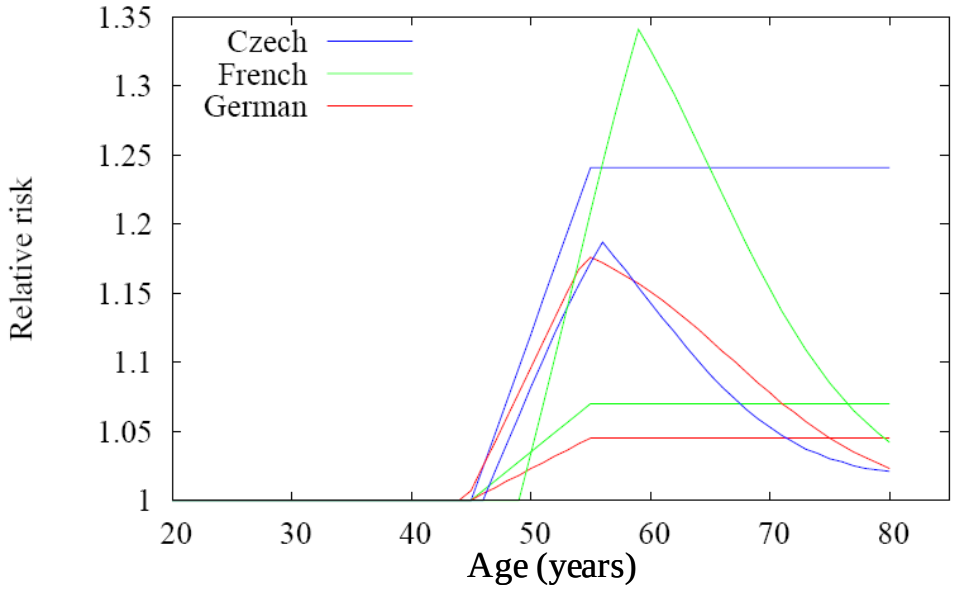

Fig. WP1.8. *Relative risk functions for an exposure to 1 WLM/year from age 40 to 50. The functions with constant relative risks at higher age are estimates from the heuristic models, the other ones from the Initiation-Promotion models.*

In a pooled analysis, the French and German data sets do not differ significantly in any of the applied parameters. For the Czech data set, only two parameters which determine the clonal expansion without radiation and with low radiation rates (promotion) are consistent with the other studies. The other parameters are significantly different. For low radiation exposure rates, the resulting relative risks are quite similar. Exposure estimates for each year of exposure are used. In addition the consequences for risk are calculated for the uncertainty model from deliverable D1.7 for each yearly exposure. For the classical errors the necessary distributions of true exposures are estimated in the form of Weibull distributions with parameters adjusted such that the distribution of recorded exposures is described as good as possible.

The changes due to the exposure uncertainties are mostly of minor importance, except that the large difference in the radiation-induced initiation between the studies is decreased substantially.

1.2.7. Analysis of risk among miners using organ dose calculation

Miners are subjected to multiple sources of exposure depending on the mining environment and atmosphere. Especially, miners are chronically exposed to different types of radiation: radon (Rn) gas, radon decay products (progeny), external gamma rays and long-lived radionuclides (LLR). However it is extremely difficult in risk analyses to discriminate the contribution to the total risk attributable to each type of radiation exposure. The aim of Deliverable D1.8 was to analyse the risk of death from cancer in relation to the organ dose due to these three sources of exposure. A dose calculation software has been developed by WP5 specifically for that purpose. The excellent collaboration between WP1 and WP5 allowed the first study to analyse the risk of cancer in relation to organ dose among miners to be conducted. This work was done by IRSN with major involvements of NRPI for risk modelling, and BfS and WP5 dosimetrists for the characterisation of past exposures.

The study population included uranium miners from the French, Czech and German cohorts described in D1.1&1.3, except for the French cohort which was restricted to miners employed

after 1956 and except for the German cohort where 90 subjects were excluded because exposure to gamma and LLR could not be assessed. A total of 48 350 miners was finally included. The distribution of the three exposures was analysed in detail. Significant correlations between the three exposures were observed in each cohort.

Methodology for organ dose calculation is described in WP5 deliverables (Marsh et al. Rad Prot Dosim 2008). The calculation is based on the implementation of ICRP models, taking into account the specificities of exposures in mines atmospheres. A large amount of work was done by WP1 and WP5 to characterize the mines atmosphere for different period since the beginning of uranium extraction, to determine specific work-type profiles, and to propose pertinent parameters for the dosimetric model. The Alpha Miner software was developed by WP5 partners specifically for that study. This software was then applied to each miner form the European joint cohort to estimate the doses due to each of the four exposures. Deliverable D1.8 presents, for each cohort, the distribution of absorbed doses (in Gy) due to alpha and non alpha emitters to the lung, kidney, red bone marrow (RBM) and liver, as well as the contribution of radon gas, radon progeny and LLR to the alpha dose. Equivalent organ doses (in Sv) were estimated using a weighting factor of 20 for alpha emitters.

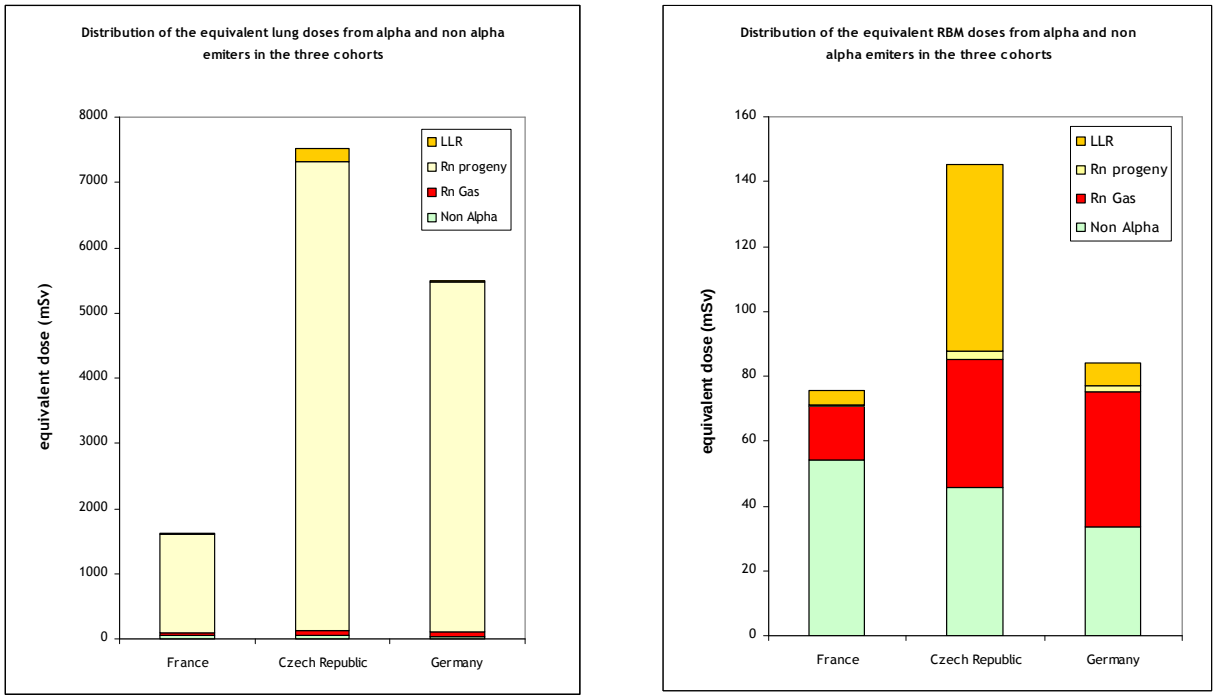

***Fig. WP1.9**. Distribution of the equivalent* doses from alpha and non alpha emitters in the three cohorts for lung (left part) and Red Bone Marrow (RBM, right part) (weighting factor of 20 for alpha emitters).*

Figure 1.9 shows the estimated doses to the lung and to RBM. For the same exposures, doses to the lung are much higher than those to RBM. For each organ, different patterns were observed between cohorts, reflecting differences in the levels of exposure. But more drastically, Figure 1.9 illustrates the differences in the respective contribution of each source of exposure between organs. For lung, the dose was essentially attributable to radon progeny, whereas for RBM, the contribution of radon progeny was negligible and the part due to gamma rays, radon progeny or LLR was much more important.

The dose-risk relationships between the cumulated equivalent organ dose and the excess relative risks (ERR) of death from lung, kidney, liver cancer or leukaemia were assessed by

Poisson regressions using background rates estimated internally with stratification on study, age, and calendar year. Analyses were performed on the European joint cohort.

The main result was the positive and significant ERR of lung cancer associated to the total equivalent lung dose (ERR/Sv = 0.07 [0.06–0.08]). Positive and significant ERRs were also observed for non alpha and alpha lung doses (Rn gas + Rn progeny or LLR alpha). Nevertheless, total dose is due to more than 96 % to Rn progeny and this contribution therefore explains most of the excess risk observed among the European uranium miners. When adjusted regressions were performed to take into account the contributors to organ dose simultaneously, only the ERRs associated to alpha lung doses remained significant. Similar associations were observed as well in each of the three cohorts.

The second result concerns leukaemia. A significant association between leukaemia risk and the total equivalent RBM dose was observed (ERR/Sv = 3.7 [1.1–8.8]). Positive and significant ERR were also observed for non alpha and alpha RBM doses (Rn gas + Rn progeny or LLR alpha). When considering separately chronic lymphatic leukaemia (CLL) and non-CLL, both were positively associated to total equivalent RBM doses (Figure 1.10). No clear relationship was found between kidney or liver cancer risk and the corresponding equivalent organ dose.

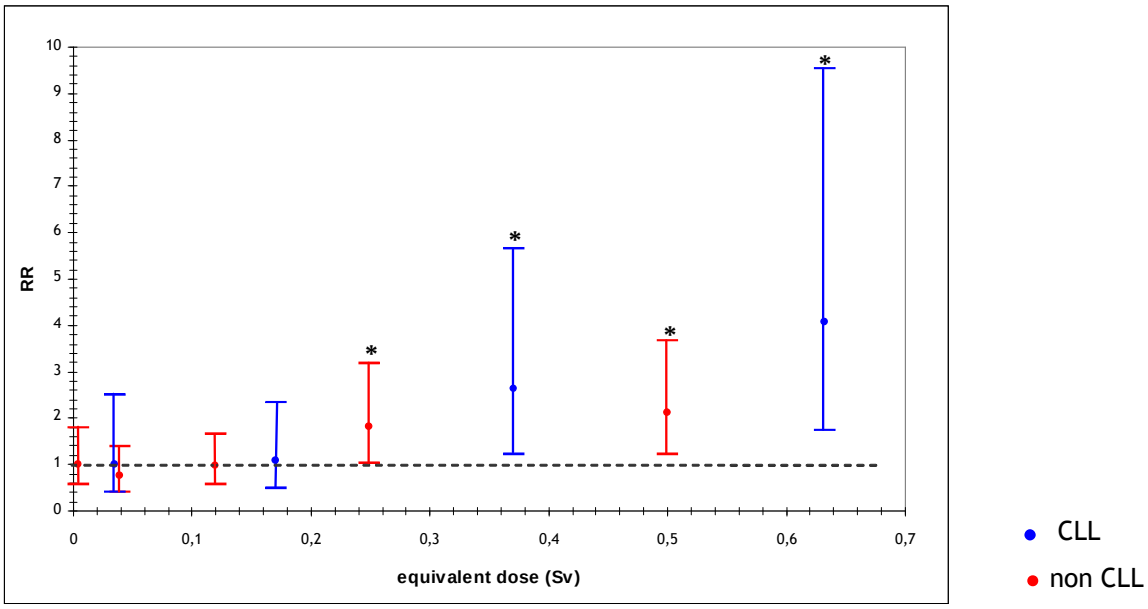

Fig. WP1.10. *Relative risk of Chronic Lymphoblastic Leukaemia (CLL) and non-CLL in dependence on categories of cumulated equivalent RBM dose in the European joint cohort.*
(90% confidence intervals derived from the floating absolute risk method; * $p < 0.05$)

In conclusion, application of the organ dose is a method of assessing the risk related to multiple sources of chronic exposures. This study is the first one to analyse the risk of cancer in relation to organ dose among uranium miners. Results show a significant increase of lung cancer risk with lung equivalent dose, attributable mainly to the alpha components of the dose. An increase of leukaemia risk with RBM equivalent dose is also observed, but radon is not the main contributor to the equivalent dose. The present results should be considered as preliminary and further analyses are currently being performed.

1.2.8. Case-control study of leukaemia risk among German miners

Lung cancer is a well known effect on uranium miner's health from exposure to radon. However little is known about the effect of ionizing radiation on incidence of the different types of leukaemia in miners. Moreover, miners usually participate in occupational check-up programs including Chest-X-ray examinations. The aim of the present study was to re-examine leukaemia risk among miners by also taking into account the exposure to X-rays from diagnostic and screening procedures. This work was conducted by BauA, in collaboration with WP5 partners for organ dose calculation.

Data from a previously analyzed individually matched case-control study of former uranium miners in East Germany were used. The study considered a total of 377 cases and 980 controls. Additionally, data on X-ray examinations due to diagnostic examinations were extracted from medical records in the WISMUT Health data archive for most of all subjects. Finally, the absorbed dose to red bone marrow (RBM) due to occupational and diagnostic exposure was calculated, using the AlphaMiner program developed in WP5 to calculate organ doses among miners. Occupational absorbed dose took into account the contribution of cumulated exposures to radon gas, radon decay products, and external gamma rays and ore dust long-lived radionuclides.

The mean absorbed dose to the RBM due to occupational exposure was 23.6 mGy (26.3 mGy in cases and 22.5 mGy in controls). Nearly three quarters of this dose was accumulated more than 15 years ago. External gamma radiation contributed approximately two thirds of the total absorbed dose to the RBM due to occupational exposure, whereas the inhalation of radon gas alone was about 28%, and about 3% aroused from the inhalation of radon progeny alone and only about 2% from the inhalation of LLR. The mean absorbed dose to the RBM due to all diagnostic X-ray examinations was 23.5 mGy, i.e. in the same range as those due to occupational exposure. The mean values for cases and controls were similar (24.6 mGy and 23.1 mGy respectively). About half of this dose was produced by diagnostic chest X-ray examinations.

Analyses were conducted using conditional logistic regression models. A moderately but not statistically significant elevated relative risk (estimated by the Odds ratio OR) was seen in the dose category above 200 mGy for the combined dose from both sources (OR=1.33, 90%-CI:[0.82–2.14]). Ignoring the dose accumulated in the recent 20 years, the estimated relative risk in the highest dose category (>105 mGy) was even higher (OR=1.77, 90%-CI:[1.06–2.95]). Ignoring diagnostic exposure yielded similar results. For the highest dose category (absorbed dose lagged by 20 years) the risk was more then doubled (OR=2.64, 90%-CI:[1.60–4.35]).

In conclusion, the results of this very important case-control study suggest that leukaemia risk among uranium miners is influenced not only by recent exposures to ionizing radiation. Moreover, exposure to medical X-rays, especially Chest-X-rays does not seem to be negligible in the discussion about leukaemia risk.

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Work package 2: Indoor radon studies

Work Package Leader: **ISS, F. Bochicchio**
Participants: Helmholtz Zentrum München, UOttawa

2.1 Context and work package objectives

Pooled analyses of residential case-control studies represents the most precise and accurate estimate of the lung cancer risk due to radon exposure in dwellings, due to the large number of subjects included in the analyses and the capability to control for a number of possible confounding studies (Lubin et al. 2004, Darby et al. 2005, 2006, Krewski et al 2005, 2006).

The impact of these studies on regulations and policies has been considerable: several national and international organizations have recently updated (or have planned to update) their recommendations to take into account the results from epidemiological studies on residential radon exposure (e.g. WHO 2009, ICRP 2009).

Moreover, case-control studies have allowed to evaluate the combined effects of radon and cigarette smoking, which also have a potential large impact on health policies (e.g. Bochicchio 2008, WHO 2009).

It has to be underline that risk estimates from case-control studies on residential radon exposure are highly affected by the uncertainty on the evaluated radon exposure: in particular, the risk estimate obtained in the polled analysis of the European studies doubles after correction for such exposure uncertainties (Darby et al 2005, 2006).

In this context, the general objective of this work-package is:

- To complete a joint database of worldwide data on indoor radon and lung cancer risk from case control studies in which radon concentrations have been assessed using air based measurements.
- To describe the different factors able to influence exposure characteristics in those countries involved in the joint European analysis and make a synthesis defining the most appropriate data for a risk assessment approach.
- To develop appropriate statistical methodology to adjust for random uncertainties in the assessment of radon concentrations in studies of residential radon and lung cancer.
- To develop a methodology for assessment of risks associated to low indoor radon exposure will be critically reviewed on the basis of recently published studies. These results will contribute to discussions within WP6.

2.2 Scientific results

The main scientific results have been reported in deliverables D2.2 (“Synthesis of variability factors linked to measurements and exposure characteristics in homes”), D2.3 (“Measurement error in the explanatory variable of a binary regression: regression calibration and integrated conditional likelihood in studies of residential radon and lung cancer) and

D2.4 (“Lung cancer risk assessment approach in relation to low levels of annual radon exposure”).

This report focuses on the synthesis of variability factors linked to measurements and exposure characteristics in homes. This synthesis deals with the issue of radon exposure uncertainty in epidemiological case-control studies, and particularly with the estimate of such uncertainty based on the evaluation of repeated measurements carried out in different years in the same places.

Quite few data on the repeated radon concentration measurements on different years are available, and not all of them have been published. In section 2.2.1, a detailed synthesis of published studies on year-to-year is reported, which include those summarized in Darby et al. (2006).

New (previously unpublished) results from two other datasets are included in section 2.2.2 of this report: the results of the Italian dataset analysis are reported in chapter 2.2.2.1, and the results of the Swiss dataset analysis are reported in chapter 2.2.2.2.

The yearly variability depends on many factors and parameters, including radon concentration measurement technique and procedures. Therefore, the studies on year-to-year variability to be used to correct radon measurements carried out for epidemiological studies should have ideally the same measurement technique and procedures used in the “corresponding” epidemiological studies. Otherwise, some uncertainties and biases could affect the risk adjustment procedure. Therefore, in section 2.2.3 of this report, some characteristics of radon measurement carried out in epidemiological studies have been compared to those used in the year-to-year variation studies carried out in the same region or country.

2.2.1. Review of published studies on year-to-year variations of indoor radon concentration

The knowledge on year-to-year variability of radon concentration in indoor air is generally not very large, and few studies have been published on this issue. Moreover, most of these studies do not refer to experiments specifically designed to acquire measurements of this variability, but they analyse already existing data on radon concentration (obtained for other purposes) in order to evaluate yearly variability.

The studies included in this review are quite different as regards the number and the span of years covered by measurements, with different information content. In some studies radon concentration measurements are made in many consecutive years in relatively large group of dwellings (which are the most informative studies); in other studies only two years are measured (with a gap of many years between the two measurements) in few dwellings. Notably, some studies were not specifically addressed to evaluate the year-to-year variations but only to estimate the overall change of radon concentration in a group of dwellings after a certain period of time. For these last studies the estimates of the year-to-year variation are not explicitly reported in the text. In these cases, we calculated the temporal variability using the data extracted from the scatter plots published in these studies.

For each study the yearly variability is estimated using the Coefficient of Variation (CV) of the measurements. Each study have been reviewed on the basis of the following information: a) aim of the study; b) location; c) number and characteristics of the studied dwellings; d) number of years of measurements and total span of years; e) duration of the radon measurements; f) type of detectors; g) distribution of measured radon concentrations; h)

methods of estimation of the yearly variability; i) results of estimation of the yearly variability; j) other results and interpretation/discussion of results reported in the paper.

This information has been reported for each study in D2.2, and are summarized in the Table WP2.1 (which contains also, for some unpublished studies, information reported as personal communication within the paper of Darby et al., 2006).

Moreover, the same information has been reported in Table WP2.1bis for two (Italian and Swiss) datasets (extensively analyzed in section B). Table WP2.1bis has been reported just after Table WP2.1 in order to facilitate the comparison.

In particular, in tables WP2.1 and WP2.1bis the following information are reported:

- study area
- number and type of dwellings
- dwelling selection criteria, that indicate how the study was designed
- years with repeated measurements
- time span (in years) of the radon measurements in dwellings
- number of detectors used to estimate yearly radon concentration in each house
- number of rooms where measurements were carried in each house
- typical duration of measurements in each year
- information reporting if measurements were carried out in the same rooms
- information on occupier and building changes
- information on radon concentration
- the estimate of year-to-year coefficient of variations (CV).

The year-to-year coefficient of variations in Table WP2.1 and WP2.1bis were calculated with different approaches (see deliverable 2.2). The CVs calculated using the first approach are highlighted in bold, whereas those calculated using the second approach are reported in red colour. For the second approach, the statistical models used in each paper have been reported in Section B.1.

In Table WP2.1, CVs (and 95% CIs) are reported in two columns: one for the CVs that have been reported in the original papers, the other for the CVs that we have estimated from data extracted from graphs in the paper. The CI in Table WP2.1 is not always reported in the published paper. In these cases, where it was possible, the CI has been calculated using the methods described in the deliverable D2.2.

Table WP2.1 integrates the information contained in the synthesis of the published studies reported in this section with the information reported as personal communication in Table 30 of the paper of Darby et al. (2006) for some unpublished studies.

The studies in Table WP2.1 have been grouped for studies carried out in China, Europe and North America to take into account that three different pooled analyses of case-control studies have been published so far (Lubin et al., 2004; Darby et al., 2005, 2006; Krewski et al., 2005, 2006).

Table WP2.1. *Summary of results on year-to-year variability from published studies, including also unpublished ones but reported in Darby et al. (2006) as personal communication.*

Study area (Reference)	**No. (and type) of dwellings**	**Dwelling selection criteria**	**No. of years with repeated meas.**	**Time span (years from the 1st to the last meas.)**	**No. of det. used to estimate yearly RnC**	**No. of rooms meas. for each house**	**Typical duration of meas. in each year**	**Meas. always in the same room**	**Occupier or Building changes**	**Rn concentration (Bq/m^3)**	**"Mean" Year-to-year CV (CI)**	
											Reported in the original paper	Estimated from data in the paper
											Reported in the original paper	Estimated from data in the paper
CHINA												
1- Qingyang (China) (Lubin et al., 2005)	55 (5 different types of single family dwellings)	Specifically selected for Annual Variation study	3	3	9–36	2.8 (AM) 1-6	1 year	Yes	None	348 (GM) 356 (AM)	43% (40%-46%)	
EUROPE												
2 - Sweden (Hubbard et al., 1993)	55 (houses with alum shale as building material)	From existing databases	2	35	1	1	30 min for the first subset; 3 months for the second one	N.R.	N.R.	~130 (Med)	-	43% (35%-51%)
3 - Sweden (Swedjemark et al., 1994)	32 (single family dwellings) (1)	From existing databases	2	14	1	1	30 min for the first subset; 3 month for the second one	N.R	Changes in the ventilation systems for some houses	~180 (Med)		39% (28%-50%)
	20 (multi family dwellings) (1)									~70 (Med)		65% (54%-76%)
4-UK Lomas and Green (1994)	218 (mostly single family houses)	From existing databases	2	Up to 10	2	2	Either 1 year or 3 months seasonal corrected	Not necessary	Most of the occupiers changed; dwellings with radon mitigation omitted.	191 (AM) 107 (GM) second period	51% (46%-57%)	
5-UK Hunter et al. (2005)	96 (houses selected with radon level around 100 Bq/m^3)	Specifically selected for Annual Variation study	4; 6	8	2	2	3 months	Not necessary	None	94 (GM) 110 (AM)	43% (40%-46%)	

Study area (Reference)	No. (and type) of dwellings	Dwelling selection criteria	No. of years with repeated meas.	Time span (years from the 1st to the last meas.)	No. of det. used to estimate yearly RnC	No. of rooms meas. for each house	Typical duration of meas. in each year	Meas. always in the same room	Occupier or Building changes	Rn concentration (Bq/m^3)	"Mean" Year-to-year CV (CI)	
											Reported in the original paper	Estimated from data in the paper
6 - Schneeberg (Germany) (Heid et al., 2002)	11 (mainly cellars of single family houses or laboratory)	From existing databases	5	5	2	N.R.	1 year (averaged using several consecutive month-periods)	Yes	None	~11500 (AM) ~3700 (Med)	59% (50%-70%)	
7-Czech Republic (in Darby et al ., 2006)	960 (mainly single-family houses)	N.R.	2	2	1	1	1 year	Yes	None	327 (GM)	36% (34%-37%)	
8-Finland (in Darby et al ., 2006)	301 (mostly single-family houses)	N.R.	18	N.R.	N.R.	N.R.	Mostly 2 months during winter, but some 1 year	Not necessary	Same occupier; buildings with radon mitigation excluded	319 (GM)	62%	
9 - Finland (in Darby et al., 2006)	80 (mostly single-family houses)	N.R.	4.2 (AM)	N.R.	N.R.	N.R.	Mostly 1 year, but some 2 months during winter	Not necessary	No occupier changes; building changes in 7 dwellings	196 (GM)	36% (33%-39%)	
10 - Sweden (in Darby et al., 2006)	44 (mostly single family houses)	N.R	Up to 13	N.R.	N.R.	N.R.	3 months in winter	Yes	None	178 (GM)	39%	
NORTH AMERICA												
11-USA (Grand Junction) Martz et al. (1991)	40 (30% of the houses were built with uranium mill tailing)	Not specifically selected for Annual Variation study	Up to 6	6–7	1.5 (AM)	1.4 (AM)	1 year	Yes	None	92 (AM) 69 (Med)	25% (2) (21%-29%)	

Study area (Reference)	No. (and type) of dwellings	Dwelling selection criteria	No. of years with repeated meas.	Time span (years from the 1st to the last meas.)	No. of det. used to estimate yearly RnC	No. of rooms meas. for each house	Typical duration of meas. in each year	Meas. always in the same room	Occupier or Building changes	Rn concentration (Bq/m^3)	"Mean" Year-to-year CV (CI)	
											Reported in the original paper	Estimated from data in the paper
12-USA (Upper Midwest) Steck (1992)	14	Not specifically selected for Annual Variation study	2	2	2	2	1 year	N.R	N.R.	N.R.	22%	
	2		Up to 7	7					Heating system was changed for one house	~100 (AM)	55%	
13-USA (Iowa) Zhang et al. (2007)	196 (98 one storey, 98 two or three storey)	Specifically selected for Annual Variation study	2	2	2 (AM)	2 (AM)	1 year	Yes	Changes in some buildings. No occupier changes	176(AM) second period	15% (2)(4) (14%-16%)	
	61 (31 one storey, 30 two or three storey) (3)	Specifically selected for Annual Variation study	2	5–6	2 (AM)	2 (AM)	1 year	Yes	Changes in some buildings. No occupier changes	184 (AM) third period	24% (2)(4) (20%-28%)	
14-USA (Minnesota) Steck (2009)	98 (mostly with basement partially below ground level)	Specifically selected for Annual Variation study	10 (Med) 3-19	13 (Med) 4-19	2(AM)	2 (AM)	1 year	Yes	Occupier changes for 18 dwellings	120 (GM) 150 (AM)	28% (2)	

AM = Arithmetic mean; Med = Median; GM = Geometric mean; N.R. = Not Reported in the paper
(1) Some houses have alum-shale as building materials.
(2) CVs were calculated for each site of the houses. So the average CV refers not to the houses, but to all sites measured.
(3)These 61 houses are a subgroup of the 196 houses for which a third measurement was carried out.
(4) CV was estimated for each floor level by house type.

Table WP2.1bis: *Summary of results of unpublished studies (described in section B)*

Location and Reference	**No. (and type) of dwellings**	**No. of years with repeated meas.**	**No. of yearly meas. for all the houses**	**No. of detectors for each houses**	**Total No. of radon meas.**	**Typical duration of measurements in each year**	**Meas. always in the same room**	**Occupier or building changes**	**Rn concentration (Bq/m^3)**	**"Mean" year-to-year CV (CI)** Estimated (Section **Erreur ! Source du renvoi introuvable.**, this report)
1-Italy (see section B)	84 (65 multi-family buildings)	8 (AM) 3–10	288	8–16	1742	6+6 consecutive months	Yes	Occupier changes for 5 dwellings	106 (AM) 84 (GM)	15% (a) (b) (14%-17%)
2-Switzerland (see section B)	21 (mostly one storey houses)	3-13	200	1.7 (AM)	927	3+3+3+3 consecutive months (+)	Yes	One house with radon mitigation	330 (AM) 264 (GM)	48% (a)(c) (37%-59%)

AM = Arithmetic mean
(a) Arithmetic mean of the CV distribution (CVs were expressed as ratio of SD to arithmetic mean for each house).
(b) CVs calculated for houses with up to 10 yearly measurements.
(c) Excluding cellars from the evaluation of radon concentration.
(+) For some houses, measurements were carried out only in winter season. These measurements were annualized using correcting factors derived in section C.2 from measurements with all seasons measured.

Data reported in Table WP2.1 can be here analyzed in order to evaluate if and how different characteristics of the studies may influence the year-to-year variability. When evaluating the influence of a specific characteristic on the CV value, the other characteristics of the study should be kept the same, condition that cannot be satisfied in this context. Furthermore, CVs were calculated using different statistical methods, and this also influences the comparison.

Therefore, it is not straightforward to find which are the main factors that influence year-to-year radon variability, and also how these factors affect the variability. Nevertheless, some rough comparisons regarding the different characteristics of the various studies has been done. In particular it has been analyzed how CV is influenced by: a) radon concentration; b) duration of the radon measurements; c) number of detectors used to estimate yearly radon concentration; d) dwelling selection criteria; e) number and span of years.

The detailed results are reported in the deliverable D2.2 and summarised as follows:

a) CVs seems to be slightly higher for higher concentrations; however, the difference is not high and no conclusion can be derived, especially taking into account that many other factors could affect this result.

b) Datasets for which duration of radon measurement is significantly lower than one year have a slightly higher CV respect to datasets for which annual radon concentration is performed with one-year long measurement. Again, no strong conclusion can be derived from this analysis, due to its intrinsic limitation.

c) This comparison does not show large differences, but no conclusion can be derived, as in the other similar analysis of this section B.2. Some conclusion could be derived only from an internal analysis of studies using duplicate measurements.

Some studies have used an estimate of measurement error to subtract its contribution to the observed year-to-year CV, in order to obtain a better estimate of the true year-to-year variations, as reported in section B1. For example, Martz et al. (1991), considering the effect of the measurement error, corrected the average CV from 25% to 22%, whereas Steck (2009) adjusted the average CV from 28% to 24%. This can give an idea of the possible impact of the number of detectors.

d) This simple analysis seems to indicate that the datasets taken from studies specifically designed for estimation of the yearly variability have a lower CV respect to datasets taken from studies with different design. However, also for this concern, no strong conclusion can be derived from this analysis, due to its intrinsic limitation.

2.2.2. Analyses of unpublished data on year-to-year variations of indoor radon concentration

In this section, unpublished results obtained from two different studies are presented.

The two datasets analysed consist of:

1) radon measurements carried out during 3 up to 10 years in about 80 dwellings mostly located in Rome (Italy), in a study specifically designed to evaluate both short- and long-term annual variations of radon concentration in dwellings
2) radon measurements carried out during 3 up to 13 years in 21 dwellings in 8 different Swiss cities.

2.2.2.1. Analysis of Italian dataset

Systematic radon measurements have been carried out since 1996 in a sample of about 80 dwellings spread in all the territory of Rome, with some dwellings located in other towns of the Rome province.

The selected dwellings include different types of buildings (mainly multi-family buildings, but also some single-family houses) with different characteristics.

For each dwelling, at least two rooms, a living room and a bedroom, were monitored. In multi-story dwellings, at least one room in each level was monitored. Non-inhabited rooms (i.e. cellars) were excluded from analysis.

The study is still on-going and data collection relative to the 13th year of study has been completed.

Radon concentration was measured by using SSNTD based radon passive devices, each containing two LR 115 detectors, in a closed configuration that prevents radon and thoron decay products to enter the sensitive volume of the device and strongly reduce the entry of thoron. The LR 115 based passive radon devices have been exposed for consecutive 6-month periods.

For each dwelling, a single annual average radon concentration is used in this analysis, obtained by averaging the values relative to: i) the two LR115 detectors included in each passive radon device, ii) the two 6-month periods in a year, in this case a weighted radon concentration mean was used, weighting the radon concentration in each 6-month period with the number of days, iii) the two or more rooms monitored for each dwelling.

Statistical and experimental methods are fully described in D2.2.

The analysis of Italian dataset is divided in four parts:

- analysis of the first 5-year period (1996–2001), to estimate short-term variations in the first 5-year period.
- analysis of the second 5-year period (2001–2006), to estimate short-term variations in the second 5-year period
- analysis of the whole 10-year period (1996–2006), to estimate long-term variations in the 10-year period
- analysis of the whole 10-year period (1996–2006) by house type, to evaluate if the observed CVs are different for different house type, particularly dwellings close to the ground (i.e. single-family houses, or apartments at ground floor) compared with dwellings far from the soil (i.e. apartments at floor levels higher than the first floor).

Analysis of the first 5 years of exposure have been published recently (Bochicchio et al 2009). A paper reporting the results of the other analyses is in preparation. All the results have been reported in D2.2 and are here summarised in the following six Figures (from B- to B-3b) and in Table WP2.2.1.

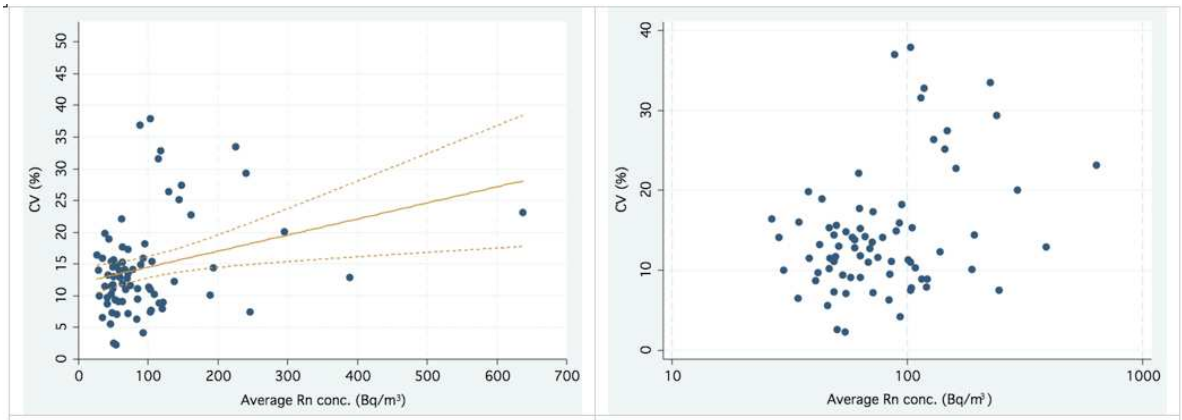

Figure B-1: CV vs Average Rn concentration (first 5-year period) (of 3-5 12-month measurements)

Figure B-1b: CV vs Average Rn concentration on log-scale (first 5-year period) (of 3-5 12-month measurements)

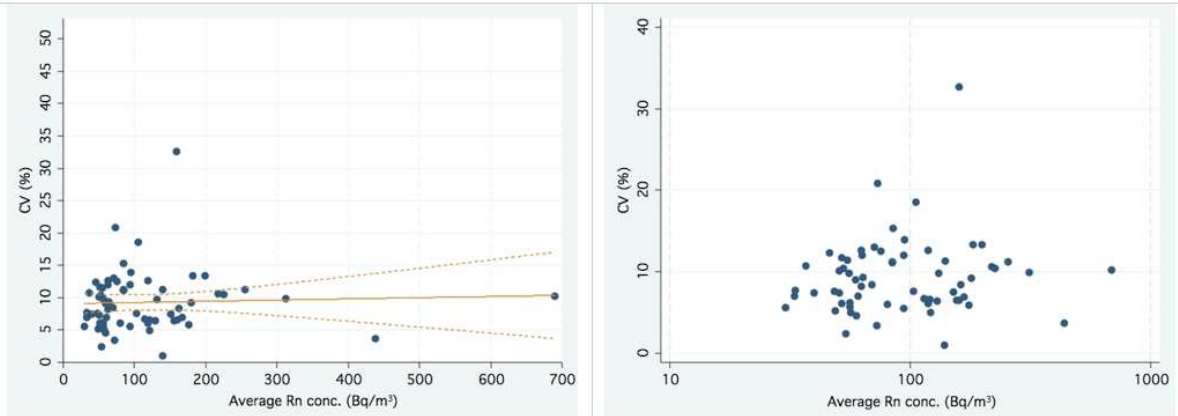

Figure B-2: CV vs Average Rn concentration (second 5-year period) (of 3-5 12-month measurements)

Figure B-2b: CV vs Average Rn concentration on log-scale (second 5-year period) (of 3-5 12-month measurements)

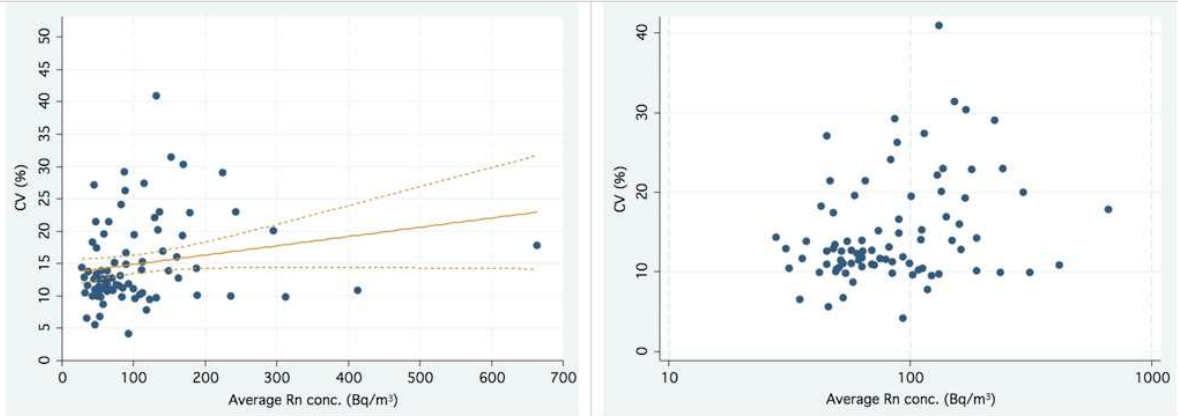

Figure B-3: CV vs Average Rn concentration (10-year period) (of 3-10 12-month measurements)

Figure B-3b: CV vs Average Rn concentration on log-scale (10-year period) (of 3-10 12-month measurements)

Table WP2.2.1: *Comparison between year-to-year coefficients of variation*

Reference time period	Estimation method		
	First approach		Second approach
	Average CV (%) (95% CI)	Median CV (%)	CV (%) (95% CI)
First 5-year period	14.4 (12.7 – 16.2)	12.9	18.8 (17.3 – 20.5)
Second 5-year period	9.3 (8.1 – 10.4)	8.4	12.1 (11.0 – 13.2)
Overall 10-year period	15.4 (14.2 – 17.2)	13.2	18.7 (17.7 – 19.8)

Results reported in Table WP2.2.1 show that confidence intervals of CV obtained following the two different approaches (described in D2.2) never overlap, emphasizing the relevance of CV computational method used.

Similar analyses as before are repeated grouping dwellings on the basis of proximity to the ground in order to find out how the different house type could influence the resulting CV.

In Italian dataset, 17 dwellings are close to ground (single-family houses or apartments at ground floor) – henceforward called “strong contact” dwellings, whereas 42 dwellings are far away the ground (second floor or higher) – “weak contact”. The remaining 25 dwellings are in an “intermediate” situation (e.g. first floor in apartment buildings) so they have been excluded from this analysis.

From Figure B-4 and from the relative summary tables it can be observed that the CV distribution is very similar in the two dwelling groups; also the average and median CVs are almost the same for the two groups.

Figure B-5 highlights that dwellings belonging to the two different groups do not form two distinct clusters.

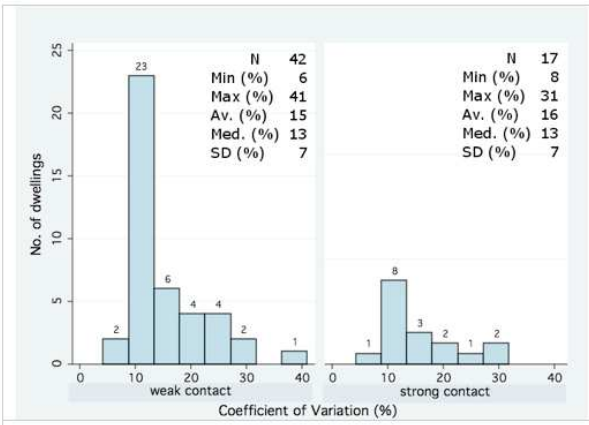

Figure B-4: Distribution of CV by house type (10-year period) (of 3–10 12-month measurements)

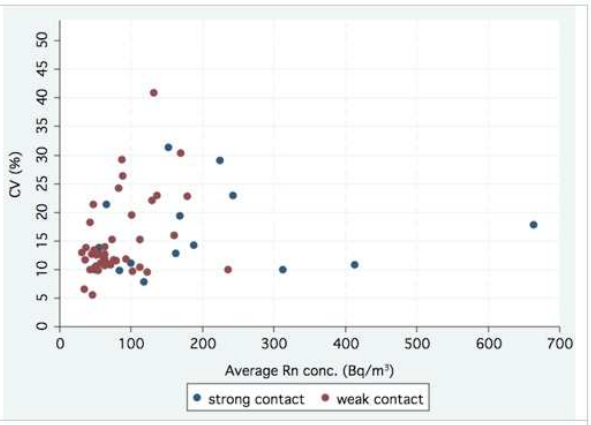

Figure B-5: CV vs Average Rn concentration by house type (10-year period) (of 3–10 12-month measurements)

2.2.2.2 Analysis of a Swiss dataset

Data included in this analysis regard 21 dwellings located in different Switzerland cities (la Chaux-de-Fonds, Krattigen, Interlaken, Danis, Breil/Brigels, Disentis/Mustér, Lü, Wädenswil). These data were kindly provided by Dr. Murith, chief of the Section of radiological risk of the Swiss Federal Office of Public Health.

Radon measurements have been carried out in 1 up to 6 rooms per each house and included different room type (living room, kitchen, cellars, etc.) located in different floor levels. In these rooms seasonal measurements (four values per year) were performed from 1991 to 2004 with the aim to collect data useful to evaluate year-to year variation of radon concentration.

In summary, complete annual measurements (4 consecutive 3-month periods for each year) were available for 14 dwellings, whereas incomplete annual measurement were available in 7 dwellings. Missing measurements were estimated using seasonal ratios derived from complete measurements.

Some results on coefficient of variations (SV) are reported in tables WP2.2.2 and WP2.2.3. It can be seen that CV for houses with incomplete annual measurements show higher CVs.

Table WP2.2.2: *Descriptive statistics of the year-to-year CV in the 14 houses where radon concentrations were available for each season of the year (including or not cellars in the estimation).*

CV	**With cellars (total)**	**Without cellars**
No. houses	14	14
Min (%)	11	11
Max (%)	71	95
Med. (%)	44	36
Av. (%)	42	42
SD (%)	23	25
GM (%)	34	35
GSD	2.0	1.9

Med=median; Av= arithmetic mean, SD=standard deviation; GM= geometric mean; GSD=geometric standard deviation

Table WP2.2.3*: Descriptive statistics of the year-to-year CV using all the 21 houses, i.e. including the extrapolated annual averages (including or not cellars in the estimation).*

CV	With cellars (total)	Without cellars
No. houses	21	21
Min (%)	11	11
Max (%)	113	113
Med. (%)	49	46
Av. (%)	48	48
SD (%)	24	25
GM (%)	42	41
GSD	1.8	1.8

Med=median; Av= arithmetic mean, SD=standard deviation; GM= geometric mean; GSD=geometric standard deviation

2.2.3. Comparison of radon measurement characteristics between epidemiological and annual variation studies

As seen previously, year-to-year variability can be used to adjust the risk assessment of epidemiological studies. Nevertheless, the yearly variability (such as the year to year CVs listed in section A) depends on the characteristics of the studies. For each country, if the epidemiological studies have been designed with different characteristics respect to the studies performed to estimate the year-to-year variability, other sources of uncertainties (e.g. due to different duration of radon measurements carried out in epidemiological studies in respect to annual variation studies) can affect the exposure variability and the risk adjustment procedures.

In this section, the characteristics of the epidemiological studies respect to the annual variation studies it has been compared. The comparison has been done only for those studies that were performed approximately in the same country or in neighbouring geographic area. In particular, the following information has been reported in Table WP2.3:

- duration of the measurement
- radon dosimeter type
- radon concentrations (geometric and arithmetic mean).

For the country where more than one study (epidemiologic and/or annual variations) were carried out, two or more values are reported.

With the aim to estimate the year-to-year variability to be applied to correct lung cancer risks observed in case-control studies, the ideal condition would be to perform repeated radon measurements:

- in a representative subgroup of the same dwellings where radon concentration was measured for the epidemiological study, and
- using the same radon measurement technique and procedures.

As regards the first condition, only two studies fulfilled it. They were carried out in Gansu Province (China) (Lubin et al. 2005) and in Iowa (Zhang et al. 2007).

As regards the second condition, only the studies carried out in Gansu Province, Iowa and Italy fulfilled it. All the other studies had some differences between the procedures used for epidemiological and those used for the annual variation studies. For example, in some epidemiological studies radon measurements were carried out with different sampling time with respect to year-to-year variation studies:

- in the case-control studies in Finland (nationwide) and Stockholm, 12-month integrated radon measurements were carried out, whereas the duration of the measurements was shorter for the correspondent year-to-year variation studies (mostly 2 months and 3 months, respectively)
- in the case-control study in South-West England, six-month integrated radon measurements were used, together with a correction factor to obtain an annual average, whereas the duration of the measurements for correspondent year-to-year variation studies was of 3 months with a correction factor to obtain an annual average (Hunter et al., 2005), and 3 and 12 months (Lomas and Green, 1994).

Regarding the dosimeter type, it seems that there are no differences between epidemiological and annual variation studies, at least for the studies where this information is reported.

Table WP2.3: *Comparison between radon measurement characteristics in epidemiologic (Ep.) and year-to-year (A.V.) variation studies*

Epidemiological study (reference)	**Corresponding study on year-to-year radon variations (reference)**	**Duration of measurements (months)**		**Radon dosimeter type**		**Radon concentration Bq/m3 (GM)**		**Radon concentration Bq/m3 (AM)**	
		Ep. study	A.V. study	Ep. study	A.V. study	Ep. study	A.V. study	Ep. study	A.V. study
Shenyang (China) (Blot et al., 1990)	Gansu (China) (Lubin et al. 2005)	12	12	CR39	CR39	91	348	116	355
Gansu (China) (Wang et al., 2002)	Gansu (China) (Lubin et al. 2005)	12	12	CR39	CR39	176	348	223	355
Pluton (Czech. Rep.) (Tomasek et al., 2001)	(Hulka and Tomasek) (a)	12	12	LR115 (Open)	unspecified □-track detectors	441(b)	327	500(b)	-
Finland nationwide (Auvinen et al. 1996, 1998)	(Makelainen) (a)	12	Mostly 2 some 12	Makrofol	N.R.	80(b)	196	96	-
South Finland (Rousteenoja et al., 1996)	(Makelainen) (a)	2	Mostly 2 some 12	Makrofol	N.R	175(b)	196	213	-
Eastern Germany (Kreuzer et al., 2003)	Schneeberg (Germany) Heid et al. (2002)	12	12	Makrofol	N.R	65(b)	~3730	74	~11500
Iowa (USA) (Field et al., 2000)	Iowa (Zhang et al. 2007)	12	12	CR39	CR-39	89	130(d)	127	81-258
Winnipeg (Canada) (Letourneau et al., 1994)	Minnesota (f) (Steck, 2009)	6+6	12	CR39	CR-39	-	120	142	150
South west England (Darby et al., 1998)	UK (Hunter et al. 2005; Lomas and Green, 1994)	6(f)	3(e), 12 (Lomas and Green) 3(e) (Hunter et al.)	CR39	CR-39	36(b)	107 (Lomas and Green) 94 (Hunter et al.)	55(b)	191 (Lomas) 110 (Hunter)
Sweden I (Pershagen et al. 1994)	Falk(a)	3 (in winter)	3 (in winter)	CR39	N.R.	72(b)	178	107	-
Sweden II (Lagarde et al., 2001)	Falk(a)	3 (in winter)	3 (in winter)	CR39	N.R.	58(b)	178	79	-
Stockholm (Sweden) (Pershagen et al. 1992)	Falk(a)	12	3 (in winter)	CR39	N.R.	119(b)	178	128	-
Lazio (Italy) (Bochicchio et al. 2005)	Rome (Bochicchio et al. (this report))	6+6	6+6	LR115	LR115	93(b)	85(c)	107	106

(GM) = Geometric Mean, (AM) = Arithmetic Mean, N.R. = Not reported, (a) Personal communication in Darby et al, 2006; b) Time weighted average (TWA) of radon; (c) From Italian studies carried out over 10 years (section 2.2.21, this report); (d) Weighted mean of the medians estimated for one- and two-story houses in Iowa (Table 2 in Zhang a. al., 2007); (e) Seasonally corrected to obtain an estimate of the annual average; (f) Winnipeg is a state close to Minnesota concentration (from Table 5 in Darby et al., 2006.)

Regarding the radon concentrations, it can be seen that in some annual variation studies the geometric mean radon concentration was more than three time higher than that of the epidemiological study, e.g. Finland nationwide (196 against 80 Bq/m^3), Shenyang (348 against 91 Bq/m^3), Sweden II (178 against 58 Bq/m^3), and especially East Germany (about 3700 against 65 Bq/m^3).

Conclusion

This report contains a review of 14 published studies, dealing with 17 different datasets, and new analyses of a large Italian study specifically designed to evaluate year-to-year variability of radon concentration and of a previously unpublished Swiss dataset. Moreover, a comparison of radon concentration measurement characteristics of these studies with those in case-control studies on lung cancer and radon exposure in dwelling hs been reported.

In conclusion, both the review of the published studies and the results of the new analyses of the Italian and Swiss datasets show that the year-to-year variability of radon concentration is quite different among studies, with a CV ranging from about 15% to about 65%.

Some partial explanation of these differences have been found (e.g. exposure time and study design) but, considering the quite different methods used in these studies, an adequate and formal comparison cannot be carried out.

Moreover, some studies are informative of short-term variations only (i.e. variation within 2–3 years), other studies are informative of long-term variations only (i.e. variation between 10 or more years), whereas just few studies are informative of both short- and long-term variations of radon concentration.

Considering that the aim of this report is to review and update information on year-to-year variability of radon concentration as a proxy of radon exposure uncertainty in case-control studies in order to correct the observed risk and obtain an unbiased estimate of the true risk, we can conclude that the correction has to be done case-by-case to try to take into account the quite different results reviewed in this report. Moreover, there are often large differences in the radon concentration measurement characteristics between studies on year-to-year variability and the corresponding case-control studies. Therefore, a sensitivity analysis is suggested to evaluate the effect of such differences on the estimated corrected risk.

Finally, considering that three different pooled analyses of epidemiological case-control studies have been published regarding studies carried out in China, Europe, and North America, it could be interesting to group all the annual variation studies of this report using the same areas, i.e. China, Europe and North America (see Table WP2.4):

Table WP2.4*: CVs information reported for studies grouped in different areas (i.e. China, Europe, and North America)*

Area	No. of studies	Median CV (%)	Range of CV(%)
China	1	43	
Europe	11	43	15–65
North America	4	24	15–55

For the 1 dataset included in the study performed in China, the CV is 43%. For the 12 datasets included in the 11 studies performed in Europe, the median CV is 43% and it ranges from 15% to 65%. For the 6 datasets included in the 4 studies performed in North America, the median CV is 24% and it ranges from 15% to 55%.

In summary, CVs appears to be lower for studies performed in North America respect to those performed in Europe and in China. Therefore, we can expect that correcting the lung cancer relative risk observed in North-American epidemiological studies for radon exposure uncertainty would produce a lower increase of the estimated relative risk than the corresponding increase obtained with such correction for the European and the Chinese studies. These results will be useful for the world pooled analysis of all the epidemiological studies.

2.3 Productions

Deliverables

Antignani S, Venoso G, Bochicchio F. Deliverable D2.2 “Synthesis of variability factors linked to measurements and exposure characteristics in homes”, Alpha-Risk Project (EC FP6, Project no. 516483), July 2009

Bochicchio F, Hunter N, Muirhead C, Laurier D, Tirmarche M, Tomasek L. Deliverable D2.4 “Lung cancer risk assessment approach in relation to low levels of annual radon exposure”, Alpha-Risk Project (EC FP6, Project no. 516483), November 2009

Scientific presentations

Tirmarche M, Bochicchio F. The Alpha-Risk project. Presented during the meeting for the publication of the WHO Handbook on Indoor Radon, organised by ISS in Roma (Italy) on September 21th 2009.

Publications

Published articles

Fearn T, Hill DC, Darby SC. Measurement error in the explanatory variable of a binary regression: regression calibration and integrated conditional likelihood in studies of residential radon and lung cancer. Statistics in Medicine 2008; 27(12): 2159-76

Bochicchio F., 2008. The radon issue: considerations on regulatory approaches and exposure evaluations on the basis of recent epidemiological results. Appl. Radiat. Isot. 66(11): 1561–1566.

Bochicchio F, Ampollini M, Antignani S, Bruni B, Quarto M, Venoso G., 2009. Results of the first 5 years of a study on year-to-year variations of radon concentration in Italian dwellings. Radiat. Meas. (in press), doi:10.1016/j.radmeas.2009.10.088 (Accepted on 22 Oct 2008. Available online 29 October 2009)

Articles in preparation

Bochicchio et al. Year-to-year variations of radon concentration in some Italian and Swiss dwellings. In preparation

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Work package 3: Nested case-control studies among nuclear workers

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3.1 Context and WP3 objectives

Studies of workers in the nuclear industry have, up to now, mainly focused on the health effects of exposure to external photon radiation. However, workers employed in some facilities – particularly facilities involved in the fuel cycle – are potentially exposed not only to photons, but also to internal radiation from a number of radionuclides such as uranium and plutonium. Little information is available on the long-term health effects of exposure to plutonium (Pu) and uranium (U) isotopes. Studies of nuclear industry workers are therefore of interest for radiation protection research because they allow the *direct* evaluation of health effects of exposure to internal radiation.

This WP aimed to investigate in detail lung cancer risk and leukaemia risk among nuclear industry workers exposed to internally deposited radionuclides. 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 (ICS), coordinated by IARC. This multinational retrospective cohort study followed up the mortality of 600,000 nuclear industry workers in 15 countries. The ICS analyses focused only on external photon radiation, excluding from the analysis workers who had potential for exposure to internal contamination. These exclusions were motivated by the fact that measurement of occupational radiation doses resulting from internal intake of long-lived transuranic nuclides is much more complicated than measurement of external photon radiation and had varied substantially over time and across facilities. It was not possible, therefore, within the framework of a large multinational cohort study to estimate adequately the individual doses from these nuclides for all workers potentially exposed. The case-control design used in this WP allowed detailed dose reconstruction as well as the collection of individual data on potential confounders, in particular smoking.

The objective of the case-control studies 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, occupational external radiation doses and other potential confounders.

3.2 Scientific results

To have sufficient statistical power to address the study objectives, nuclear workers from the 5 main European nuclear facilities (located in Belgium, France, and United Kingdom) where workers had potential for internal incorporation of U and/or Pu, as follows:

- Belgium – SCK.CEN cohort;
- France – Commissariat à l'Energie Atomique and Compagnie de Gestion des Matière Nucléaires (CEA-COGEMA) cohorts;
- United Kingdom – Atomic Energy Authority (UK-AEA) cohort;
- United Kingdom –Atomic Weapons Establishment (UK-AWE) cohort; and,
- United Kingdom –British Nuclear Fuels (UK-BNFL) cohort.

3.2.1. Assessment of Availability and Quality of Data

Prior to implementation of the study, an assessment of the necessary data was conducted to ensure a sufficient amount of data of reasonable quality was available to address the study objectives. For some certain types of data such as demographic data (e.g., date of birth and sex), employment history (e.g., start and stop dates of work by facility), and external dose data (e.g., annual doses by facility), the quality and availability was already known because of previous experience with the 15-country study that used the same study population. The objective of the assessment in WP3 was focused on data specifically needed for WP3 that were not previously used in the 15-contry study. The type of data assessed included, in particular, bioassay data (e.g., urine and faecal samples) needed for internal dose reconstruction as well as important risk factor information (e.g., smoking, chemical exposure, and chest x-ray information) for lung cancer and leukaemia that can potentially confound study results. The assessment showed that while the available data were not perfect, a sufficient amount of reasonable quality data was available to address the research objectives of WP3. Details of the assessment are documented in Deliverable 3.1 - “Report describing availability of data”.

3.2.2. Common Study Protocol and Country Specific Procedures

For WP3, a common study protocol for the case-control studies of lung cancer and leukaemia among nuclear industry workers was developed. It documented the methods agreed upon by the Study Group for the conduct of the studies. The purpose of the common protocol was to ensure consistency in subject recruitment and compatibility of data collection across facilities. It also described the organization of the study by explicitly outlining the role of the coordinating centre (CREAL), Study Group, Sub-committees (Epidemiology and Dosimetry), the use of data collected, publications, and declaration of potential conflicts of interests. The Study Protocol was reviewed and approved by the Ethics Committee of the IARC and, upon transfer of the study coordination from IARC to CREAL, by the Ethics Committee of CREAL. The detailed protocol and procedures are available as Deliverable 3.2: “Protocol and country procedures”

3.2.3. Dose Reconstruction Methods

Valid estimates of internal doses are of primary importance for WP3 as they provide the basis for valid risk estimates of lung cancer and leukemia among nuclear workers.

As such, a Dosimetry Committee was assembled and charged with the important task of developing a suitable common approach for estimating internal doses from plutonium and uranium based on available historical bioassay data from the different participating facilities The Dosimetry Committee also addressed the characterization and quantification of errors in resulting reconstructed doses. Two documents were produced as a result:

- Deliverable 3.3: “Dose reconstruction method”
- Deliverable 3.5: “Model for errors in doses”

In addition to the above protocols, a facility-specific document was also produced to document the approaches and assumptions used in the dose reconstruction (non-deliverable) of each facility. Specifically, this document describes the treatment of bioassay data and rationale for the various assumptions made, including scattering factors, correction factors, plant fingerprints, and solubility assumptions for different isotopes.

Finally, the Dosimetry Sub-committee needed to modify an existing software programme to allow dose reconstruction with the common dose reconstruction approach within WP3 and also created a new software programme for the dosimetric uncertainty analyses. Both of these tasks required tremendous amount of person days to complete. The two software programmes are:

- IMBA Professional (modified for Alpha Risk)
- Uncertainty Analyser (new software)

3.2.4. Subject Recruitment and Data Collection

Details of subject recruitment and data collection are described in Deliverable 3.6 - ‘Final Data Collection Report’. This document describes site-specific procedures used to select study subjects and also presents details of the data collected for study subjects from each facility.

In total, data from 561 lung cancer deaths and their 1,340 matched controls were collected in the lung cancer case-control study and data on 46 leukemia deaths and their 109 matched controls were in the leukaemia case-control study. Table 1 shows the number of cases and controls recruited for WP3 stratified by facility. More than half of the cases and controls were recruited from BNFL.

3.2.5. Epidemiologic Data

The final epidemiologic data file contained anonymised data on collected and coded information for all eligible cases and controls. These include data on date of birth, sex, employment history, smoking, external radiation doses, chest X-rays, chemical exposures, and vital status.

Table WP3.2 shows a summary of demographic characteristics of study subjects by facility and selection status (i.e. case or control). Almost all of the workers recruited were males, which is typical of the sex distribution among past nuclear workers in the facilities with Pu and U exposure. In all facilities, the average age at first employment in these facilities was above 30 years of age.

Table WP3.3 describes employment characteristics of recruited subjects. Estimates of duration of employment were derived from annual employment records for each worker. For Belgium, UK-AEA, and UK-AWE, cases and controls were, on average,

employed for similar amounts of time. However, for France and BNFL, cases appeared to be employed for a shorter duration of time than their matched controls.

Table WP3.1: *Summary of number of cases and controls by facility*

Study Cohort		Cases	Controls	Total
Belgium	Total	13	23	36
	Lung	13	23	36
	Leukaemia	0	0	0
France	Total	19	42	61
	Lung	17	37	54
	Leukaemia	2	5	7
UK (AEA)	Total	114	127	241
	Lung	104	117	221
	Leukaemia	10	10	20
UK (AWE)	Total	121	242	363
	Lung	113	226	339
	Leukaemia	8	16	24
UK (BNFL)	Total	340	1,015	1,355
	Lung	314	937	1,251
	Leukaemia	26	78	104
Total		***607***	***1,449***	***2,056***

Table WP3.4 provides a summary of information on cumulative external doses for study subjects by cohort. Average cumulative doses show significant variation among the five facilities. In France, the cumulative doses were less than 5 mSv for both cases and controls. For BNFL, cumulative doses were above 100 mSv for both cases and controls. Average doses per year were also estimated by dividing cumulative doses by duration of external dose monitoring. Based on data received, workers from France had the lowest average annual doses (< 1 mSv/year) compared to BNFL where workers were experiencing average annual doses that were in excess of 6 mSv/year.

Data on smoking history of workers are presented in Table 5. Approximately 67% of all workers reported as ‘Ever’ smokers. Among the ‘Ever’ smokers, duration and intensity (i.e., light, moderate, and heavy) of smoking were further quantified. The distributions of these are shown in Table WP3.5.

Almost all workers had taken chest x-rays during their employment. The numbers of recorded occupational chest x-rays received by workers are shown in Table WP3.6. On average, Belgium workers had the highest number of chest x-rays as compared to workers from UK-AEA who had the lowest number of chest X-rays. However, Belgium workers were generally employed longer than other cohorts.

3.2.6. Internal Dosimetry Data

In this study, individual doses to the lung and the active bone marrow arising from exposure to uranium (U), plutonium (Pu) and other isotopes have been reconstructed for all study participants. Doses were reconstructed by dosimetrists from each facility in consultation with the Dosimetry subcommittee. Doses have been estimated for 4 regions of the lung:

- BBSec - Lung bronchial secretory region
- BBBase - Lung bronchial basal region
- bb - Lung bronchiolar region
- AI - Lung aveolar region
- RBM - Red bone marrow.

Summary (mean, median, minimum, and maximum) of internal doses are provided in Tables WP·.7 to WP3.10. Internal doses tended to follow a skewed distribution (see Figures 1 and 2). Doses to the lung tended to be higher than doses to the bone marrow, particularly for uranium (Tables WP3.7 to WP3.11 and Figures WP3.1 and WP3.2).

Table WP3.2: *Characteristics of study subjects*

Characteristics		Belgium		France		UK-AEA		UK-AWE		UK-BNFL	
		Cases (n=13)	Controls (n=23)	Cases (n=19)	Controls (n=42)	Cases (n=114)	Controls (n=127)	Cases (n=121)	Controls (n=207)	Cases (n=340)	Controls (n=1015)
Year of Birth											
	Mean	1925.69	1926.43	1938.32	1940.24	1920.49	1919.84	1919.96	1920.14	1918.04	1918.16
	(SD)	(8.01)	(7.68)	(11.68)	(10.51)	(10.85)	(10.65)	(9.07)	(9.30)	(11.35)	(11.23)
	Range	1910-1937	1910-1939	1916-1965	1915-1965	1895-1957	1896-1957	1897-1964	1898-1964	1888-1960	1887-1960
Sex (%)											
	Male	100.0%	100.0%	100.0%	100.0%	98.2%	98.4%	95.9%	96.6%	99.1%	99.2%
	Female					1.8%	1.6%	4.1%	3.4%	0.9%	0.8%
Age at First Employment											
	Mean (SD)	33.83 (9.09)	32.74 (8.38)	36.80 (10.07)	31.05 (8.83)	39.19 (10.16)	39.42 (10.71)	38.66 (10.07)	38.45 (10.60)	38.54 (10.10)	37.51 (9.99)
	Range	21.48-51.68	22.93-58.27	20.57-55.74	21.49-55.20	17.17-61.17	20.12-61.82	16.11-60.60	16.13-60.54	16.17-64.76	16.17-61.75

Table WP3.3: *Employment characteristics by cohort and selection status*

Characteristics	Belgium		France		UK-AEA		UK-AWE		UK-BNFL	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Year of Start of First Employment										
Mean	1959.62	1959.22	1975.26	1971.43	1959.74	1959.28	1958.60	1958.57	1956.56	1955.68
(SD)	(2.63)	(4.80)	(9.01)	(9.43)	(7.44)	(7.32)	(7.77)	(8.23)	(9.78)	(9.06)
Range	1957-1965	1954-1973	1958-1986	1954-1990	1946-1981	1946-1984	1949-1981	1947-1981	1946-1987	1945-1987
Year of Stop of Last Employment										
Mean	1984.23	1985.65	1992.26	1996.19	1978.02	1978.37	1979.41	1979.76	1972.75	1971.65
(SD)	(4.57)	(5.24)	(9.39)	(8.79)	(9.16)	(9.29)	(7.20)	(7.02)	(12.94)	(12.63)
Range	1975-1990	1975-1998	1970-2003	1973-2006	1959-2000	1958-2005	1963-1993	1960-1993	1949-1999	1949-1996
Total Duration-Employment History [1]										
Mean	24.49	26.21	17.09	25.61	17.36	19.05	23.37	25.26	15.75	21.32
(SD)	(5.55)	(6.20)	(8.60)	(10.65)	(9.52)	(10.40)	(11.25)	(12.29)	(10.66)	(15.25)
Range	13.33-31.58	6.75-36.42	1.97-29.75	5.75-64.67	1.22-36.94	1.05-43.52	3.40-50.37	1.33-53.56	1.08-42.59	1.00-55.84
Social Economic Status										
1 (Least Educated)	15.4%	4.8%	10.5%	14.3%	0.9%	0.8%	6.6%	18.4%	89.1%	80.2%
2	15.4%	19.0%	5.3%	4.8%	9.6%	12.6%	14.9%	16.9%	10.9%	19.8%
3	7.7%	14.3%	63.2%	54.8%	3.5%	9.4%	9.1%	10.1%		
4	38.5%	33.3%	21.1%	26.2%	19.3%	24.4%	30.6%	16.9%		
5	23.1%	28.6%			59.6%	44.9%	34.7%	33.3%		
6 (Highly Educated)					7.0%	7.9%	4.1%	4.3%		

Note:
1. EmplStopYear variable was missing for 251 records; based on End of Follow-up Year, variable EmplStopDate was set to 01-07-2002 to estimate Duration of Employment.

Table WP3.4: *Summary of external dose (mSv) information by cohort and selection status*

Characteristics	Belgium		France		UK-AEA		UK-AWE		UK-BNFL	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Year at first monitoring										
Mean (SD)	1960.77 (2.05)	1960.30 (3.70)	1972.32 (6.95)	1971.05 (6.09)	1960.71 (7.19)	1960.65 (7.29)	1962.30 (8.07)	1963.01 (8.40)	1957.35 (9.79)	1956.46 (9.14)
Range	1958-1965	1957-1973	1967-1986	1967-1990	1948-1981	1948-1984	1949-1983	1948-1986	1946-1987	1946-1987
Year at last monitoring										
Mean (SD)	1980.77 (4.25)	1983.78 (6.33)	1988.00 (9.44)	1992.29 (6.50)	1977.95 (9.44)	1978.13 (10.26)	1980.46 (8.10)	1982.26 (8.05)	1971.84 (13.25)	1971.99 (12.90)
Range	1974-1988	1973-1994	1969-1998	1973-2003	1959-2000	1958-2007	1964-1995	1964-2002	1949-1998	1949-2000
Duration of monitoring										
Mean (SD)	20.54 (5.50)	23.65 (7.42)	14.74 (7.58)	20.05 (7.37)	17.47 (9.63)	18.07 (10.81)	18.18 (9.63)	18.80 (10.04)	14.63 (10.31)	15.70 (10.45)
Range	10-30	7-37	1-27	4-31	2-40	2-48	1-41	1-45	1-42	1-43
Cumulative dose										
Mean (SD)	75.23 (234.24)	123.41 (191.02)	1.39 (5.88)	0.09 (0.30)	110.97 (178.77)	116.95 (161.73)	30.46 (46.89)	31.05 (44.70)	110.39 (187.99)	116.63 (194.88)
Range	0.06-851.81	0.38-585.03	0.00-25.66	0.00-1.52	2.55-1676.40	1.22-811.54	0.17-355.78	0.31-283.73	0.47-1352.25	0.30-1875.79
Average cumulative dose per year (mSv/year)										
Mean (SD)	2.68 (7.79)	4.98 (7.81)	0.08 (0.33)	0.00 (0.01)	5.84 (7.38)	6.07 (6.74)	1.66 (2.63)	1.59 (1.99)	6.50 (7.38)	6.50 (7.69)
Range	0.00-28.39	0.02-24.16	0.00-1.43	0.00-0.07	0.51-67.06	0.51-31.29	0.08-22.24	0.10-12.25	0.36-39.77	0.15-48.57

Table WP3.5: *Summary of smoking information by data source and selection status*

Characteristics	Belgium		France		UK-AEA		UK-AWE		UK-BNFL	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Smoking Status										
Never	7.7%	43.5%	5.3%	4.8%	2.6%	18.9%	5.0%	25.1%	---	---
Never or Ex-smoker	---	---	5.3%	38.1%	2.6%	2.4%	3.3%	6.3%	4.1%	19.8%
Ever	92.3%	56.5%	89.5%	54.8%	75.4%	46.5%	73.6%	55.1%	89.7%	71.4%
Unknown	---	---	---	2.4%	19.3%	32.3%	18.2%	13.5%	6.2%	8.9%
Smoking Duration (years) [1]										
Mean (SD)	9.71 (11.15)	7.96 (9.91)	9.62 (6.79)	15.36 (7.83)	8.72 (9.83)	8.99 (8.71)	9.47 (11.67)	8.06 (10.43)	12.69 (12.62)	13.33 (12.81)
Range	0.50-27.00	0.50-28.00	0.50-18.00	1.00-32.00	0.50-38.00	0.50-33.00	0.50-36.00	0.50-38.00	0.50-50.00	0.50-61.00
Missing (n)	0	0	0	1	4	8	2	10	17	84
Smoking Level* [1]										
Light	---	---	---	---	1.2%	8.5%	7.9%	17.5%	2.3%	2.8%
Moderate	---	---	35.3%	13.0%	2.3%	1.7%	37.1%	30.7%	9.9%	6.9%
Heavy	---	---	11.8%	4.3%	1.2%	---	13.5%	4.4%	2.6%	0.6%
Unknown	100.0%	100.0%	52.9%	82.6%	95.3%	89.8%	41.6%	47.4%	85.2%	89.8%
Missing (n)	12	13	9	19	82	53	37	54	259	651

Note: *Based on Dr. Keith Binks' smoking protocol (Deliverable D4.3 of WP4)

1. Only Ever Smokers are considered to report Smoking Level and Smoking Duration.

Table WP3.6: *Summary of chest X-ray information by data source by selection status*

Characteristics		Belgium		France		UK-AEA		UK-AWE		UK-BNFL	
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Chest X-ray											
	Ever	100.0%	100.0%	100.0%	100.0%	95.6%	88.2%	85.1%	88.4%	98.8%	100.0%
	Unknown	---	---	---	---	4.4%	11.8%	14.9%	11.6%	1.2%	---
Number of chest X-rays											
	Mean (SD)	21.69 (5.79)	24.48 (6.12)	17.37 (8.25)	20.71 (9.97)	6.40 (7.24)	6.22 (8.85)	18.46 (8.38)	18.70 (8.64)	15.86 (12.39)	17.04 (11.42)
	Range	12-30	7-38	1-28	1-38	1-36	1-55	2-38	1-44	1-76	1-76

Table WP3.7: *Summary of cumulative internal doses (mGy) for Belgium nuclear workers*

Belgium Internal Dose (mGy)

Isotope	Selection Status: Cases	Controls
A1	0	2
C2	1	0
P1	0	3
P8	8	19
U8	8	17

Legend

A1	Americium (Am 241)	BBSec -	Lung bronchial secretory region
C2	Curium (Cm - 242)	BBBase -	Lung bronchial basal region
P1	Plutonium (Pu-241)	bb -	Lung bronchiolar region
P8	Plutonium (Pu - 238)	AI -	Lung aveolar region
U8	Uranium (U - 238)	RBM -	Red bone marrow

ISOTOPE=P8

Cumulative Internal dose (mGy) from Isotope P8 to the lung regions and red bone marrow

	Site	Lung Cases (n=8)				Lung Controls (n=19)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	0.0000	0.0000	0.0000	0.0000	1.0442	0.0000	0.0000	15.0589
	BBBase	0.0000	0.0000	0.0000	0.0000	0.1206	0.0000	0.0000	1.7480
	bb	0.0000	0.0000	0.0000	0.0000	0.4481	0.0000	0.0000	6.5204
	AI	0.0000	0.0000	0.0000	0.0000	0.7768	0.0000	0.0000	11.8475
	Total Lung	0.0000	0.0000	0.0000	0.0000	0.5964	0.0000	0.0000	8.8346

ISOTOPE=U8

Cumulative Internal dose (mGy) from Isotope U8 to the lung regions and red bone marrow

	Site	Lung Cases (n=8)				Lung Controls (n=17)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	0.4363	0.0000	0.0000	3.4904	2.5889	0.0000	0.0000	13.9763
	BBBase	0.0410	0.0000	0.0000	0.3283	0.2430	0.0000	0.0000	1.3082
	bb	0.3554	0.0000	0.0000	2.8434	2.0986	0.0000	0.0000	11.3115
	AI	0.7896	0.0000	0.0000	6.3168	4.1205	0.0000	0.0000	21.0276
	Total Lung	0.4566	0.0000	0.0000	3.6529	2.5195	0.0000	0.0000	13.1938

ALL ISOTOPES

Cumulative Internal dose (mGy) from all Isotopes to the lung regions and red bone marrow

	Site	Lung Cases (n=13)				Lung Controls (n=23)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	0.2685	0.0000	0.0000	3.4904	3.1507	0.0000	0.0000	16.8654
	BBBase	0.0253	0.0000	0.0000	0.3283	0.3222	0.0000	0.0000	1.9265
	bb	0.2187	0.0000	0.0000	2.8434	2.0874	0.0000	0.0000	11.3115
	AI	0.4859	0.0000	0.0000	6.3168	4.0228	0.0000	0.0000	21.0276
	Total Lung	0.2810	0.0000	0.0000	3.6529	2.5894	0.0000	0.0000	13.1938

Table WP3.8: *Summary of cumulative internal doses (mGy) for French nuclear workers*

France Internal Dose (mGy)

Isotope	Selection Status	Cases	Controls
	P1	14	28
	P9	14	29
	P1/P9	14	29
	U4	17	34
	P1/P9/U4	19	42

Legend

P1 - Plutonium (Pu - 241)
P9 - Plutonium (Pu - 239)
U4 - Uranium (U - 234)

BBSec - Lung bronchial secretory regi
BBBase - Lung bronchial basal region
bb - Lung bronchiolar region
AI - Lung aveolar region
RBM - Red bone marrow

Cumulative Internal dose (mGy) from plutonium (**P1 and/or P9**) to the lung regions and red bone marrow

	Site	Lung Cases (n=12)				Lung Contols (n=25)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	20.2918	0.0000	0.0000	205.4613	1.6319	0.0000	0.0000	18.6005
	BBBase	1.8735	0.0000	0.0000	18.6687	0.1550	0.0000	0.0000	1.8550
	bb	10.3150	0.0000	0.0000	105.9777	0.8024	0.0000	0.0000	9.2039
	AI	20.3829	0.0000	0.0000	232.0926	1.1901	0.0000	0.0000	20.0713
	Total Lung	13.9268	0.0000	0.0000	150.0441	0.9620	0.0000	0.0000	13.0041
RBM		Leukaemia Cases (n=2)				Leukaemia Contols (n=4)			
	RBM	0.0430	0.0430	0.0000	0.0859	0.0000	0.0000	0.0000	0.0000

Cumulative Internal dose (mGy) from uranium (**U4**) to the lung regions and red bone marrow

	Site	Lung Cases (n=15)				Lung Contols (n=30)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	2.0974	0.0000	0.0000	24.4233	0.5236	0.0000	0.0000	8.6823
	BBBase	0.1565	0.0000	0.0000	1.8205	0.0415	0.0000	0.0000	0.6520
	bb	1.1539	0.0000	0.0000	13.4356	0.2890	0.0000	0.0000	4.7768
	AI	0.4267	0.0000	0.0000	4.9671	0.1102	0.0000	0.0000	1.7700
	Total Lung	0.9025	0.0000	0.0000	10.5082	0.2273	0.0000	0.0000	3.7386
RBM		Leukaemia Cases (n=2)				Leukaemia Contols (n=4)			
	RBM	0.0105	0.0105	0.0000	0.0210	0.0000	0.0000	0.0000	0.0000

Cumulative Internal dose (mGy) from Plutonium (**P1 and/or P9**) and/or uranium (**U4**) to the lung regions and red bone marrow

	Site	Lung Cases (n=17)				Lung Contols (n=37)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	16.1743	0.0000	0.0000	205.6313	1.5272	0.0000	0.0000	18.6005
	BBBase	1.4606	0.0000	0.0000	18.6687	0.1383	0.0000	0.0000	1.8550
	bb	8.2994	0.0000	0.0000	105.9777	0.7767	0.0000	0.0000	9.2039
	AI	14.7644	0.0000	0.0000	232.0926	0.8935	0.0000	0.0000	20.0713
	Total Lung	10.6270	0.0000	0.0000	150.0441	0.8343	0.0000	0.0000	13.0041
RBM		Leukaemia Cases (n=2)				Leukaemia Contols (n=5)			
	RBM	0.0538	0.0538	0.0216	0.0859	0.0000	0.0000	0.0000	0.0000

Table WP3.9: *Summary of cumulative internal doses (mGy) for nuclear workers from UK-AEA*

UK-AEA Internal Dose (mGy)

Selection Status

Isotope	Cases	Controls
Ac7	1	0
P1	98	99
P9	98	99
Pa1	0	1
Po1	2	2
R6	1	2
T2	0	3
T8	1	1
U4	80	96
P1/P9	98	99
P1/P9/U4	114	127
All	114	127

Legend

Ac7	Actinium (Ac - 227)	BBSec -	Lung bronchial secretory region
P1	Plutonium (Pu - 241)	BBBase -	Lung bronchial basal region
P9	Plutonium (Pu - 239)	bb -	Lung bronchiolar region
Pa1	Protactinium (Pa - 231)	AI -	Lung aveolar region
Po1	Polonium (Po - 210)	RBM -	Red bone marrow
R6	Radium (Ra - 226)		
T2	Thorium (Th - 232)		
T8	Thorium (Th - 238)		
U4	Uranium (U - 234)		

Cumulative Internal dose (mGy) from plutonium (**P1**) to the lung regions and red bone marrow

	Site	Lung Cases (n=90)				Lung Contols (n=90)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	0.0310	0.0034	0.0000	0.6506	0.0149	0.0040	0.0000	0.2544
	BBBase	0.0081	0.0014	0.0000	0.1548	0.0039	0.0015	0.0000	0.0595
	bb	0.0751	0.0044	0.0000	2.1728	0.0276	0.0051	0.0000	0.6040
	AI	0.8022	0.0196	0.0000	30.2545	0.2577	0.0320	0.0000	6.2638
	Total Lung	0.2989	0.0088	0.0000	10.8759	0.0982	0.0139	0.0000	2.3416
RBM		Leukaemia Cases (n=8)				Leukaemia Contols (n=9)			
	RBM	0.0500	0.0463	0.0002	0.1109	0.0314	0.0153	0.0000	0.1282

Cumulative Internal dose (mGy) from plutonium (**P9**) to the lung regions and red bone marrow

	Site	Lung Cases (n=90)				Lung Contols (n=90)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	23.0070	2.1833	0.0002	1157.9600	15.5327	3.3995	0.0014	721.4961
	BBBase	2.0637	0.2036	0.0000	104.3950	1.3895	0.3030	0.0001	64.9824
	bb	11.4670	1.0723	0.0001	587.8286	7.6807	1.6310	0.0007	365.8447
	AI	20.2673	1.3452	0.0002	1186.6100	12.7323	2.0270	0.0011	730.9183
	Total Lung	14.7564	1.1403	0.0001	801.8676	9.6247	1.9312	0.0009	496.6640
RBM		Leukaemia Cases (n=8)				Leukaemia Contols (n=9)			
	RBM	1.0400	0.8078	0.0041	3.0783	0.7067	0.7297	0.0043	1.5874

Cumulative Internal dose (mGy) from plutonium (**P1 and/or P9**) to the lung regions and red bone marrow

	Site	Lung Cases (n=90)				Lung Contols (n=90)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	23.0380	2.1870	0.0002	1158.2100	15.5475	3.4040	0.0014	721.6976
	BBBase	2.0718	0.2042	0.0000	104.5498	1.3934	0.3038	0.0001	65.0274
	bb	11.5421	1.0749	0.0001	590.0014	7.7083	1.6352	0.0007	366.3051
	AI	21.0695	1.3734	0.0002	1216.8700	12.9901	2.0697	0.0012	735.6041
	Total Lung	15.0554	1.1532	0.0002	812.7435	9.7229	1.9660	0.0009	498.4205
RBM		Leukaemia Cases (n=8)				Leukaemia Contols (n=9)			
	RBM	1.0900	0.8870	0.0043	3.1892	0.7381	0.7745	0.0047	1.7085

Cumulative Internal dose (mGy) from uranium (**U4**) to the lung regions and red bone marrow

	Site	Lung Cases (n=72)				Lung Contols (n=89)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	23.0257	0.4721	0.0000	643.0146	9.0122	0.3815	0.0006	174.1588
	BBBase	1.9773	0.0411	0.0000	54.3679	0.7773	0.0333	0.0000	14.6706
	bb	12.9020	0.2662	0.0000	359.4247	5.0711	0.2155	0.0003	97.3249
	AI	7.5475	0.1904	0.0000	200.8803	3.3500	0.1549	0.0002	54.3875
	Total Lung	10.9836	0.2368	0.0000	302.9971	4.4386	0.1926	0.0003	82.0419
RBM		Leukaemia Cases (n=8)				Leukaemia Contols (n=7)			
	RBM	0.0366	0.0026	0.0000	0.2340	0.0175	0.0018	0.0006	0.1032

Table WP3.10: *Summary of cumulative internal doses (mGy) for nuclear workers from UK-AWE*

UK-AWE Internal Dose (mGy)

Selection Status

Isotope	Cases	Controls
P1	1	0
P9	98	163
U4	97	154

Legend

P1	BBSec - Lung bronchial secretory region
P9	BBBase - Lung bronchial basal region
U4	bb - Lung bronchiolar region
	AI - Lung aveolar region
	RBM - Red bone marrow

ISOTOPE P9

Cumulative Internal dose (mGy) from Isotope P9 to the lung regions and red bone marrow

	Site	Lung Cases (n=92)				Lung Controls (n=155)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	28.9132	0.0024	16.1966	267.1451	22.8974	0.0000	14.4102	244.3917
	BBBase	2.6021	0.0002	1.4537	24.1013	2.0577	0.0000	1.3047	21.8835
	bb	14.5796	0.0012	8.1511	135.7832	11.4747	0.0000	7.2164	121.7571
	AI	27.9222	0.0023	15.3079	277.3672	21.0734	0.0000	14.0977	205.2183
	Total Lung	19.2256	0.0016	10.4328	184.3953	14.8584	0.0000	9.7103	151.8373
	Site	**Leukaemia Cases (n=6)**				**Leukaemia Contols (n=8)**			
	RBM	0.2915	0.0004	0.3160	0.5782	1.0459	0.0126	0.2565	5.5356

ISOTOPE U4

Cumulative Internal dose (mGy) from Isotope U4 to the lung regions and red bone marrow

	Site	Lung Cases (n=91)				Lung Controls (n=146)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	15.6888	0.0000	7.0758	201.9498	10.3232	0.0000	4.8358	223.8641
	BBBase	1.4273	0.0000	0.6417	18.3762	0.9966	0.0000	0.4430	20.4347
	bb	9.1655	0.0000	4.0877	118.0240	6.0131	0.0000	2.8305	131.1107
	AI	11.5946	0.0000	5.2454	149.8629	7.5361	0.0000	3.6561	171.6947
	Total Lung	9.6750	0.0000	4.3317	124.7565	6.3390	0.0000	3.0156	140.2351
	Site	**Leukaemia Cases (n=6)**				**Leukaemia Contols (n=8)**			
	RBM	0.05435	0.000007	0.014148	0.265788	0.020791	0.001778	0.00634	0.122734

ALL ISOTOPES

Cumulative Internal dose (mGy) from All Isotopes to the lung regions and red bone marrow

	Site	Lung Cases (n=105)				Lung Controls (n=169)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	38.9304	0.0031	25.8484	270.5827	29.9188	0.0117	23.4508	248.0879
	BBBase	3.5169	0.0003	2.3208	24.4145	2.7482	0.0011	2.0654	22.6415
	bb	20.7180	0.0018	14.0708	143.4149	15.7188	0.0065	12.2001	143.4831
	AI	34.5140	0.0021	22.9112	280.0025	25.8382	0.0097	19.1113	205.2183
	Total Lung	25.2304	0.0018	16.8214	186.5481	19.1039	0.0074	14.4249	157.3359
	Site	**Leukaemia Cases (n=7)**				**Leukaemia Contols (n=9)**			
	RBM	0.2964	0.0004	0.2717	0.5931	0.9482	0.0103	0.2992	5.5412

Table WP3.11: *Summary of cumulative internal doses (mGy) for nuclear workers from UK-BNFL*

UK-BNFL Internal Dose (mGy)

Selection Status

Isotope	Cases	Controls
P	88	336
U4	285	851
P/U4	337	1007

Legend

P Plutonium Unknown
U4 Uranium (U - 234)

BBSec - Lung bronchial secretory region
BBBase - Lung bronchial basal region
bb - Lung bronchiolar region
AI - Lung aveolar region
RBM - Red bone marrow

Cumulative Internal dose (mGy) from plutonium (**Unknown**) to the lung regions and red bone marrow

	Site	Lung Cases (n=84)				Lung Contols (n=326)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	5.2326	2.2367	0.1054	62.1744	4.6830	2.3726	0.0489	68.5450
	BBBase	1.1919	0.6080	0.0275	8.0856	1.2118	0.6550	0.0128	16.0240
	bb	2.2560	0.8806	0.0406	32.3555	1.9124	0.9511	0.0189	33.9550
	AI	2.1655	0.3116	0.0131	73.8710	1.0110	0.3395	0.0062	55.1550
	Total Lung	2.5446	0.8692	0.0400	46.7148	1.9569	0.9386	0.0186	42.1530
RBM		Leukaemia Cases (n=4)				Leukaemia Contols (n=10)			
	RBM	1.5231	1.0153	0.5428	3.5189	0.8951	0.3449	0.0919	4.4526

Cumulative Internal dose (mGy) from uranium (**U4**) to the lung regions and red bone marrow

	Site	Lung Cases (n=262)				Lung Contols (n=782)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	14.0701	4.7166	0.0064	126.0918	13.0004	5.1317	0.0064	162.6861
	BBBase	1.1783	0.4035	0.0005	10.6009	1.0897	0.4291	0.0005	13.7680
	bb	7.8550	2.6353	0.0036	70.4078	7.2576	2.8643	0.0036	90.9551
	AI	4.3808	1.4785	0.0020	39.4104	4.0378	1.5872	0.0020	50.9523
	Total Lung	6.6199	2.2240	0.0030	59.3878	6.1134	2.4153	0.0030	76.7111
RBM		Leukaemia Cases (n=23)				Leukaemia Contols (n=69)			
	RBM	0.1994	0.1076	0.0012	1.2162	0.2153	0.0857	0.0003	1.3283

Cumulative Internal dose (mGy) from Plutonium (**unknown**) and/or uranium (**U4**) to the lung regions and red bone marrow

	Site	Lung Cases (n=311)				Lung Contols (n=929)			
		Mean	Min	Median	Max	Mean	Min	Median	Max
Lung Regions	BBSec	13.2666	4.7762	0.0583	126.0918	12.1330	4.9170	0.0238	162.6861
	BBBase	1.3145	0.5403	0.0048	10.6009	1.2251	0.5250	0.0020	16.3623
	bb	7.2267	2.4056	0.0325	70.4078	6.5950	2.4403	0.0133	90.9551
	AI	4.2754	1.2078	0.0131	74.4125	3.6557	1.2841	0.0062	55.1550
	Total Lung	6.2642	2.1322	0.0271	59.3878	5.6432	2.1680	0.0112	76.7111
RBM		Leukaemia Cases (n=26)				Leukaemia Contols (n=78)			
	RBM	0.3052	0.0953	0.0003	4.6165	0.3052	0.0953	0.0003	4.6165

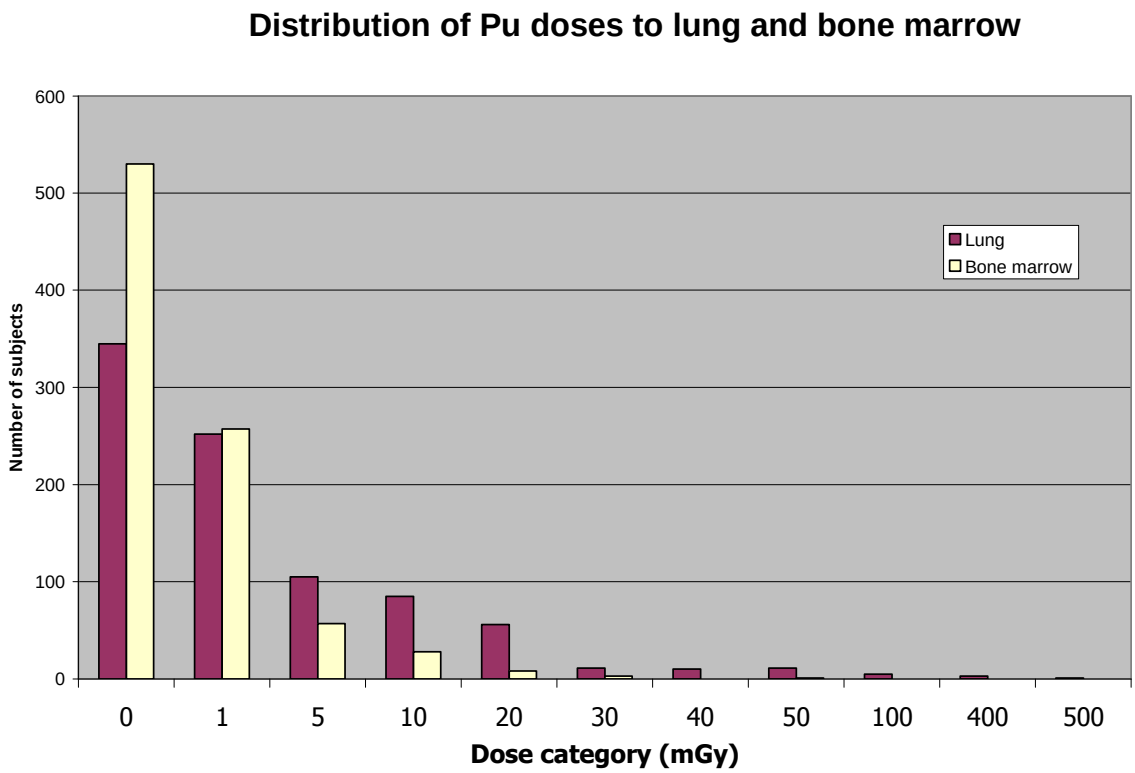

Fig. WP3.1: *Distribution of doses from plutonium intake*

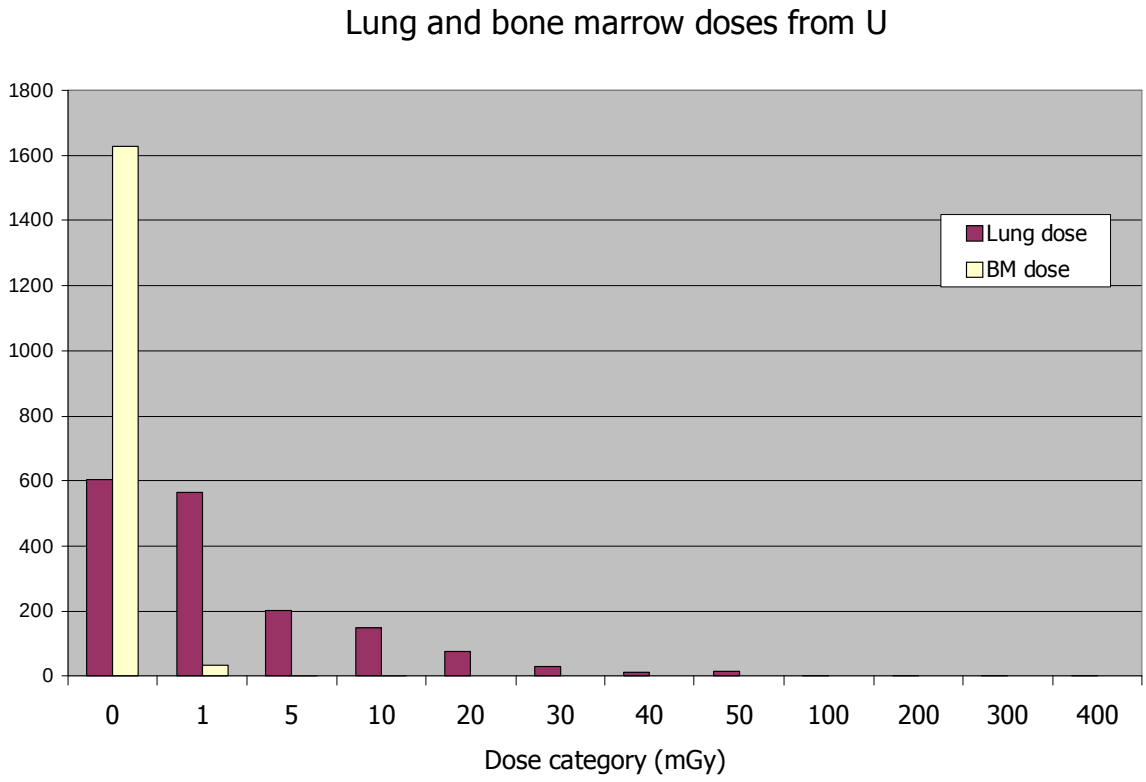

Fig. WP3.2: *Distribution of doses from uranium intake*

3.2.7. Preliminary Risk Estimates

Preliminary risk estimates have been derived based on data received to date using the linear excess relative risk model. Four models and their results are shown in Figure WP3.3. In the first model (Model 1), the excess relative risk of lung cancer was estimated in relation to cumulative dose from plutonium lagged by 10 years in order to account for latency effects. After taking the effects of external dose into account, a small and non-significant excess relative risk of lung cancer death was observed. Similar results were observed for uranium (model 2). In model 3, the independent effects of both plutonium and uranium were assessed. Again, similar results were observed as in Model 1 and 2. In the last model (Model 4), lung cancer risks from all internal doses combined were estimated. The preliminary results suggest a significant excess relative risk in lung cancer mortality of 0.008 per mGy (95%CI: 0.00045-0.0215) i.e. an ERR/Gy of 8 (95% CI 0.45-21.5), higher than, but statistically compatible with the corresponding estimate of lung cancer risk in relation to external dose estimated in the 15 country study (ERR/Gy 1.86, 95% CI 0.49-3.63). Smoking adjustments for these risk estimates are being presented in Deliverable 3.8.

Model 1: External Dose + Plutonium (all lung regions)

Variable	ERR	95% CI
External Dose (mSv)	-0.000262	-0.00063 0.0004
Plutonium (mGy)	0.008789	-0.00066 0.0351

Model 2: External Dose + Uranium (all lung regions)

Variable	ERR	95% CI
External Dose (mSv)	-0.000256	-0.00061 0.0004
Uranium (mGy)	0.006212	-0.00111 0.0221

Model 3: External Dose + Plutonium + Uranium (all lung regions)

Variable	ERR	95% CI
External Dose (mSv)	-0.000287	-0.00053 0.00036
Plutonium (mGy)	0.008927	-0.00055 0.03477
Uranium (mGy)	0.007273	-0.00108 0.02413

Model 4: External Dose + All Isotopes (all lung regions)

Variable	ERR	95% CI
External Dose (mSv)	-0.000287	-0.00065 0.00036
All Isotopes (mGy)	0.007833	0.00045 0.02151

Fig. WP3.3: *Preliminary risk estimates (per mGy) of lung cancer mortality in relation to plutonium and/or uranium doses (10-year lag).*

Preliminary risk estimates have also been derived assessing the relationship between death due to leukemia and internal exposures to plutonium and/or uranium. These estimates are presented in Models 1 to 4 in Figure WP3.4 and have been adjusted for the effects of external radiation exposures. While these results suggest a decreased excess risk, readers are advised to limit interpretations of these results as they are preliminary.

Model 1: External Dose + Plutonium (red bone marrow)

Variable	ERR	95% CI
External Dose (mSv)	6.54 *10^-05	-0.0002 0.0004
Plutonium (mGy)	-0.07142	-0.0724 -0.0704

Model 2: External Dose + Uranium (red bone marrow)

Variable	ERR	95% CI
External Dose (mSv)	6.09 *10^-05	-0.0002 0.0004
Uranium (mGy)	-0.117	-1.749 1.515

Model 3: External Dose + Plutonium + Uranium (red bone marrow)

Variable	ERR	95% CI
External Dose (mSv)	6.24 *10^-05	-0.0002 0.0004
Plutonium (mGy)	-0.07135	-0.0728 -0.0699
Uranium (mGy)	-0.1192	-1.746 1.508

Model 4: External Dose + All Isotopes (red bone marrow)

Variable	ERR	95% CI
External Dose (mSv)	6.36 *10^-05	-0.00023 0.0004
All Isotopes (mGy)	-0.07138	-0.0724 -0.0703

Fig.WP3.4: *Preliminary risk estimates (per mGy) of death due to leukemia in relation to plutonium and/or uranium doses (2-year lag).*

Studies of workers in the nuclear industry have, up to now, mainly focused on the health effects of exposure to external photon radiation. However, workers employed in some facilities – particularly facilities involved in the fuel cycle – are potentially exposed not only to photons, but also to internal radiation from a number of radionuclides such as uranium and plutonium. These groups of nuclear industry workers are of interest for radiation protection because they allow the *direct* study of health effects of exposure to internal radiation. To date, very little is known on the long term health effects of internal exposure to ionizing radiation particularly on populations exposed to plutonium (Pu) and uranium (U) isotopes. WP3 was designed to address this knowledge gap. As with many new studies, WP3 had to overcome some major challenges.

- Methods of reconstructing internal doses to specific regions of the lung and bone marrow are fairly new and needed much discussion among leading dosimetrists and statisticians in order to obtain the most reasonable estimate of internal doses; particular difficulties were related to assumptions concerning the chemical form and solubility of the radionuclides of interest in different facilities over time;
- Existing software (IMBA) needed to be modified to optimize usage of data available to WP3;
- New software (Uncertainty Analyzer, UA) was needed to conduct uncertainty analysis;
- Output files were very large (in excess of 10 gigabytes) and required special computing power;
- Significant delays in obtaining appropriate ethics approval were encountered; and,
- Significant amount of risk factor information available only in text format and needed to be recoded manually (e.g., smoking data).

Although this has been a challenging study to implement, a number of valuable lessons has been learned that will be invaluable in future studies. For example, internal dose reconstruction in WP3 has benefited greatly from the expertise of leading dosimetrists in this field. Specifically, assumptions about solubilities, scattering factors, and other parameters needed for dose reconstruction are well described in the Deliverables and will be invaluable in future dose reconstructions efforts. Development of new software to address uncertainties will also be a future asset.

While a reasonably large number (561) of lung cancer deaths were observed in this study, allowing the estimation of a dose-response relationship and the observation of a significant increased risk in relation to total internal dose, the confidence intervals are wide. A further follow-up of this study, including additional lung cancer 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.

Leukaemia, however, is much rarer than lung cancer, and only 46 leukaemia deaths were observed in this study, thus the statistical power to estimate the effect of internal exposure on the risk of leukaemia is very low. Again, further follow-up of this study, and extension to other cohorts would be important in order to provide more precise direct estimates of the effect of these exposures.

3.3 Productions

Deliverables

The following deliverables have been prepared:

- D3.1 – Report describing availability of data
- D3.2 – Protocol and country procedures
- D3.3 – Dose reconstruction method
- D3.4 – Interim report detailing status of data collection
- D3.5 – Model for errors in doses;
- D3.6 – Final data collection report;
- D3.7 – Programme for taking into account errors in doses.
- D3.8 – Report presenting design, analysis and preliminary results of nested case-control study of lung cancer; and,
- D3.9 – Report presenting design, analysis and preliminary results of nested case-control study of leukaemia.

Scientific presentations

To date, the efforts have been focused on completing the study, which was much delayed because of difficulties in obtaining ethics approvals. It is only now, that discussions on different dissemination strategies are being formalized.

- WP3 presentation from Alpha-Risk Open Meeting in Paris, October 2009 (see Appendix)

Publications

The following scientific papers are currently being considered and/or preparation:

In dosimetry

- Internal dose estimation for the case-control studies
- Uncertainties in estimated lung doses for plutonium workers
- Monte Carlo Algorithm for estimating uncertainties in internal doses.

In epidemiology

- Nested case-control studies of nuclear workers – Estimates of lung cancer risk associated with internal exposure to uranium and plutonium
- Nested case-control studies of nuclear workers – Estimates of leukaemia risk associated with internal exposure to uranium and plutonium

Work package 4: The Feasibility of a consented cohort study of mortality risks in EU plutonium and uranium nuclear workers

Work Package Leader:	**WSC, K Binks**
Work Package Secretary:	WSC, T Riddell
Participants:	IRSN (I. Canu, F. Masson, E. Samson, M. Tirmarche), HPA (A. Birshall, M. Puncher, W. Zhang, C. Muirhead), CAATS (S. Caër-Lorho, C. Maccia)

4.1 Context and work package objectives

The ultimate objective of the future cohort study is to determine cancer and non-cancer mortality risks using organ specific plutonium and uranium doses, adjusted for external doses, for the EU nuclear workers. The EU nuclear workers experience much lower levels of organ specific plutonium and external doses and dose rates than Mayak workers.

Hence the future study will produce information on mortality risks from occupational exposure to plutonium which can be compared and contrasted with risks for Mayak workers. Additionally, the study will provide key information on mortality risks from occupational exposure to uranium. A future joint study of UK (BNFL) and French plutonium and uranium workers is feasible, in principle. However, Work Package 4 of α-RISK is concerned with the Feasibility Study.

The objectives of the Feasibility Study (WP4) were to:

- Describe the current position on the consents and permissions to undertake workforce epidemiology studies
- Review the scientific literature on plutonium and uranium worker studies.
- Establish the extent and availability of the epidemiology data for the UK-BNFL (Sellafield and Springfields) and French (CEA-AREVA) plutonium and uranium worker cohorts
- Identify those data which need to be collected to fill gaps, computerised and validated, and what processing of the data is necessary to undertake the study
- Examine the compatibility and comparability of the data items on the respective databases and describe how incompatible data will be dealt with in analyses
- Describe what data will be used in the statistical analyses, describe these analyses and the statistical power of the study
- Describe the confidentiality arrangements and how the dissemination and publication of results will be dealt with

4.2 Results achieved

The outputs from these objectives collectively form the major part of the Outline Research Study Protocol (K Binks, 2009). For some of the more substantial pieces of

work reports (Binks and Samson 2008; Binks and Scott 2008; Riddell 2008), have been produced as part of Work Package 4.

4.2.1. Study Consents and permissions

CEA-AREVA workers

All consents and permissions to undertake the study have already been obtained for the 1968-2006 cohort of CEA-AREVA workers. Permission from the French Consultative Committee was obtained in February 2007 and from the French Data Protection Authority (CNIL) in May 2007.

An announcement of the study has been written and posted for all CEA and AREVA workers. No worker has chosen not to be included in the study. The consents of the Staff and Trade Unions (CHSCT) for each of the French nuclear sites were obtained during 2007 to 2009.

An ethically acceptable way has been agreed with the site occupational physicians whereby information for consented worker studies can be collected from medical records.

BNFL workers

Consents and permissions have to be obtained for the 1946-2002 cohort of BNFL workers to be included in the future study. The Research Study Protocol (RSP) has to have the support of workers and Staff and Trade Unions, together with full funding for the study. The RSP is submitted with supporting information to a Research Ethics Committee (REC) for ethical review (NRES). Given a favourable opinion from the REC, support to use the mortality data will be sought (NHS) from the national organisation which provides the mortality data.

4.2.2. Review of plutonium and uranium worker studies

Plutonium worker studies

There is clear evidence of plutonium dose-response relationships ($p< 0.001$) for lung, liver and bone cancer mortality in the Mayak studies. The most recent analysis of cancer mortality among Mayak workers (Sokolnilov 2008) reports elevated risks of cancers of the lung, liver and bone. At an attained age of 60, the ERRs per Gy for lung cancer were estimated to be 7.1 for males and 15 for females; the averaged-attained age ERRs per Gy for liver cancer were 2.6 and 29 for males and females, respectively; whilst those for bone cancer were 0.76 and 3.4. However, elevated risks for bone cancer were observed only in the 10+ Gy category (with 3 deaths). The ERR per Gy for external dose was 0.19 (95% CI=0.05-0.39) for lung cancer, but was not significant for liver or bone. There were no significant effect modifiers. An ERR per Gy for leukaemia of about 7 ($p< 0.001$) for external doses received within 3 to 5 years of death has been reported (Shilnikova 2003).

A future cohort mortality study of the EU nuclear workers would address the key question of ‘what are the mortality risks for these 4 end points using information for the 15,000 or more CEA-AREVA and Sellafield plutonium workers’.

Uranium worker studies

There is little or no epidemiological evidence for an association between uranium dose and any cancer (UNSCEAR 2006; Canu 2008). A future joint cohort study would allow the investigation of cancer and non-cancer disease specific outcomes amongst 25,000 uranium workers.

4.2.3. Extent and Availability of Epidemiology data

A substantial amount of effort has been put into establishing the extent and availability of information for uranium workers employed by the AREVA family of companies (COMURHEX, EURODIF, AREVA-NC, FBFC, SOCATRI) and for workers employed by CEA in research activities (Binks and Samson 2008). Information exists from urinalyses, faecal sampling and whole body counts from examinations performed by the SHI Laboratories. It is a matter of collecting, validating and processing the information.

Information on major potential confounders such as smoking, blood pressure, weight, etc exists in medical records for both BNFL and CEA-AREVA workers, but substantial amounts of information may be missing.

The BNFL urinalysis database and respective BNFL and CEA-AREVA databases containing occupational history, gender, birth, death and external dosimetry information already exist.

The table below gives an estimate of the likely numbers of CEA-AREVA and BNFL plutonium and uranium workers. These estimates are likely to increase.

Table WP4.1*: Estimated number of plutonium and uranium workers amongst a collaborative France-UK study*

Industry	Uranium Workers	Plutonium Workers
CEA-AREVA	16.000	5,000
BNFL	9,000	10,000
TOTAL	25.000	15,000

4.2.4. Data Gaps, Computerisation and Processing

The major information gap relates to the urinalysis database for CEA-AREVA workers. It is essential to have the existing computerised database thoroughly validated and all the missing urinalysis data collected and validated. Only when a validated urinalysis database exists for the CEA-AREVA workers can organ specific doses be computed using the methodology agreed by the EU internal dose committee (Riddell 2008).

Point estimates of lung and red bone marrow doses have been computed for the BNFL Sellafield and Springfields plutonium and uranium workers using the agreed methodology (Riddell 2008).

Some information for smoking and other potential confounding factors does exist on databases, whilst any other remaining information will be in paper records. The justification for consented collection and processing of information is that these can

be satisfactorily used in proposed studies. For BNFL workers there is and algorithm to process smoking information for use in epidemiology studies.

4.2.5. Compatibility and comparability of data items on the respective databases

A compatible set of data required for a joint mortality study of the external dose experience can be computed from the information on the respective CEA-AREVA and BNFL databases illustrated below. Point estimates of organ specific doses for the CEA-AREVA plutonium and uranium workers will be computed on the same basis as that for BNFL worker and once available can be used in the joint study.

Occupational History Information

Table WP4.2: *Summary of the available data on occupational history*

CEA-AREVA database item	BNFL database item
IndividuId	Unique Worker Identifier
Première Enterprise	Company details held within employment episode
Dernière Enterprise	
Deb_Emploi	Details of up to 6 employment episodes are held
Fin_Emploi	
Deb_Suivi	These data items are dynamically derived during
Fin_Suivi	extraction of data from the database for statistical
Deb_Sui_Dosi	analysis
Fin_Sui_Dosi	
TypeContrat	Doesn't contain contractor information
Qualification	Job Category
Filière	Category
SES	Socio Economic Status

The data for nuclear sites and periods of employment, start and end of follow up and radiation work, and a measure of socio-economic status are computable from the occupational health information.

Gender, Birth and Death Information

Gender, vital status, date of birth and underlying cause of death information is readily available for the joint study, see table WP4.3.

Table WP4.3: *Summary of the available administrative and health data*

CEA-AREVA database item	BNFL database item
IndividuId	Unique Worker Identifier
Sexe	Sex
Statut_Vital	Trace Result
DatNaiss	Date of Birth
CauseDC_Principale	Underlying Cause of Death
CauseDC_Assoc1	Contributory Causes of Death
CauseDC_Assoc2	
DepNaiss	Place of Birth
ComNaiss	
CdepDC	Place of Death
ComDC	

4.2.6. External Dosimetry Information

Both the CEA-AREVA and BNFL databases contain the annual external dose information required for the joint study. Available data are summarised in the table WP4.4.

Table WP4.4: *Summary of the available external dosimetry data*

CEA-AREVA database item	BNFL database item
Clé Primaire	Sequence number
IndividuId	Unique Worker Identifier
Periodicity	Frequency (Daily, Weekly, etc.)
An	Year
TypePort	Where worn (Body, Cap, etc.)
NomMasqueId	
Best_XG	
Best_DTE	
Best_N	
Dose1	Annualised dose is used for analysis purposes
Dose2	Both CEA-AREVA and BNFL records contain annual
Dose3	external doses
Dose4	Dose 1 - Dose 10 will contain annual X, γ neutrons, etc
Dose5	doses. The given order of the doses differs for CEA and
Dose6	AREVA worker files.
Dose7	
Dose8	
Dose9	
Dose10	
UnMes	Units are always mSv
FlagNeutron	Flags would require validation if they were to be used
Flag_Cl	
Flag_H3	
ValSeuil	Limit of detection flag
Commentaire	Comments
Enquete	
Dosi_Ant	
Lieu_Doses_Unité	Unit of dose (coded item)
Code_Lieu_Doses_Unité	
Lieu_Doses_Site	

4.2.7. Statistical Analyses and Statistical Power

Exploratory Data Analysis (EDA) (Cardis et al 1997) will be performed to ensure that the data is consistent and unusual data will be re-validated in accordance with ISO 9001:2000 standard operating procedures which are in accordance with Good Epidemiological Practice (IEA). The EDA will also examine potential confounders since in addition to age, sex and calendar year, there may be other potential confounders that should be adjusted for in the subsequent analysis. Industrial status (industrial or non-industrial, additionally categorised by administrative or non-administrative posts for French workers), a measure of socio-economic status, and employment site are two potential confounders. In addition, year of joining, length of exposure, length of service and length of follow-up will also be assessed. These covariates will be examined amongst the radiation workers as potential (Gilbert 1982; Pearce 1992) for all causes of mortality and mortality due to cancer. Adjustment for important confounders will then be made by stratification. Worker status will not be considered a potential confounder as it lies on the causal path.

Workers are followed to death or to the study cut-off date. For employees who have an ONS/ RNRNIPP trace of 'Embarked', which may signify that the person has left the country or is lost to follow–up the person is followed up only to the date of embark or last date known. If a person subsequently returns to the country the time that the person is embarked is excluded from the cohort's person years of experience.

Standardised Mortality Ratios (SMRs) will be used to compare the number of BNFL and CEA-AREVA worker cause specific cancer and non-cancer deaths with the number of expected deaths based on the respective national cause-specific mortality age-sex-calendar year rates.

To reduce some of the biases resulting from comparison with the national population rates, the cancer mortality experience of the external radiation workers will be compared with that of the other radiation worker groups and Rate Ratios (RRs) determined.

The statistical significance of the association between cause specific death and cumulative external and cumulative organ-specific internal radiation exposure will be examined using a trend test (Hakulinen et al. 1981; Mantel 1963).

For grouped Poisson analyses, the data will be categorised as follows:

- External dose: 11 dose groups will be used 0-4, 5-9, 10-19, 20-49, 50-99, 100-149, 150-199, 200-299, 300-399, 400-499, 500+, lagged 0, 2, 10, 15 and 20 years
- Organ specific doses: dose groupings as appropriate, lagged 0, 2, 10, 15 and 20 years
- Age: 15 age groups will be used 15-19, 20-24, 25-29…80-84, 85+
- Gender: male and female
- Calendar year: individual calendar years will be used.

Poisson regression models will be used to describe linear excess relative risk (Prentice and Mason 1986) and linear excess additive risk of the mortality experience associated with the organ-specific internal radiation before and after adjusting for external radiation. Type of radiation worker (internal or external), employment site, duration of exposure, age at first exposure and gender, will be examined as effect modifiers. Confidence intervals will be obtained by direct exploration of the profile likelihood function (Moolgavkar and Venzon 1987). Time since exposure will be examined using doses in time windows of 3 to 5, 5 to 10, 10 to 20 and 20+ years. 'Joint' analysis (Pierce 1993) will be used to compare the dose-response of different diseases groups.

Should the study of confounders be supported then appropriate study designs have to be considered where data is collected and processed for only a selected subset of all the workers in the cohort. Further, the issue of missing data (Borgan et al. 2000) and use of case-cohort designs (Romanov et al. 2003), with or without counter matching (Khokhryakov et al; 1998), should be considered.

Statistical Power

The statistical power of the study has been assessed by the use of the Sellafield plutonium worker urinalysis data (Table WP4.6 and Fig. WP4.1). Four different solubility parameter assumptions have been made to calculate the plutonium doses.

Two are based on the ICRP default parameters and two on the Mayak dosimetry methodologies. The four different solubility assumptions are:

M –This is based upon the ICRP default Type M (Medium) which is recommended for plutonium nitrate.

S –This is based upon the ICRP default Type S (Slow). This assumption represents the most insoluble type plutonium and will produce the highest lung doses.

R - This assumption is based upon the Mayak methodology (Romanov et al. 2003).

K – This assumption is based upon the Mayak methodology (Khokhryakov et al. 1998).

The statistical power of detecting a linear plutonium lung dose-response has been determined using Monte Carlo simulation (Richardson 2003).

Table WP4.5: *Detectable relative risk per Sv of plutonium lung dose, with 80% power for Sellafield radiation workers under various solubility assumptions*

M	S	K	R
3.78	1.03	2.35	1.14

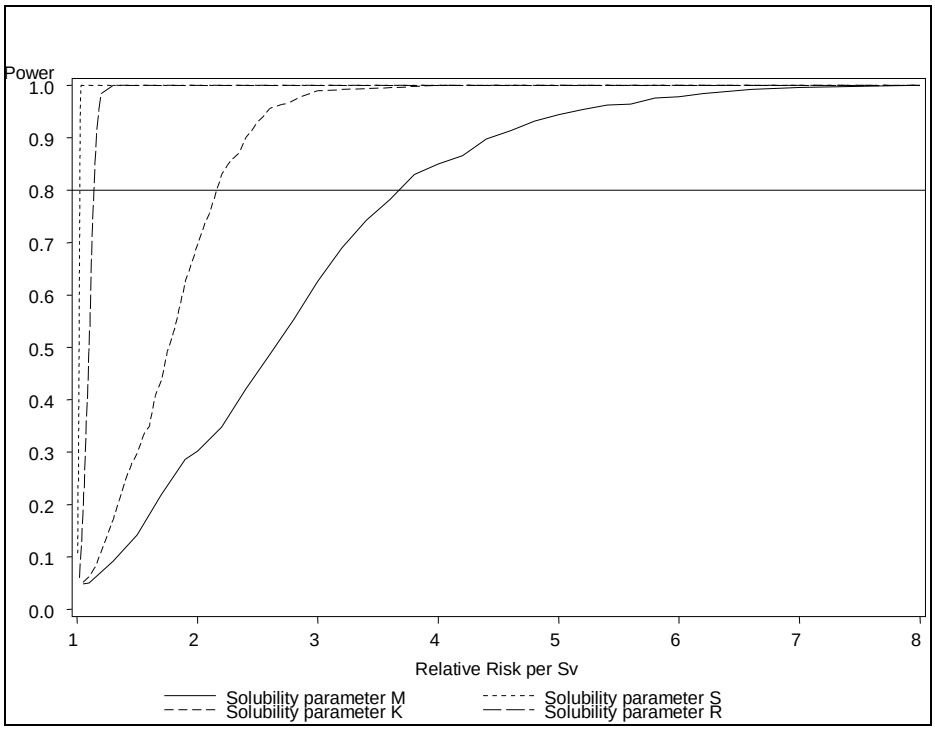

Fig. WP4.1: *Power to detect a relative risk per Sv of plutonium lung dose, with 80% power for Sellafield radiation workers under 4 solubility assumptions.*

Data Confidentiality and Dissemination of Results

The work will conducted in a way that ensures confidentiality and anonymity of the workers identity and data associated with the worker. WSC data security policy for epidemiology research is compliant with the appropriate sections of BS7799, one of the safeguards required for the PIAG exemption. The data will be extracted from these systems in a pseudo-anonymised format. No personnel identifiers (name, identification numbers, etc) will be extracted. Individuals will, however, be assigned a unique identifier in the statistical analysis files to ensure traceability to the source records to resolve any inconsistencies that may be found in the data.

IRSN is the data controller for the French nuclear worker epidemiology database. The data custodian receives the data from the occupational health department of the different companies involved in the study. The data will be held on a private dedicated network which requires password access to the data and has been validated by the French Data Protection Authority (CNIL). For the statistical analyses, the data will be extracted from the private network and sent to the medical co-ordinator of each company. The medical co-ordinator will add the cause of death, extract all the personal identifiers (name, identification numbers, etc) and replace them with a unique key identifier.

The analysis will, therefore, be done using pseudonymised data.

The findings of the study will be written up and submitted for peer-reviewed publication in a high quality journal. There will be presentations of the results as required by the Staff and Trade Unions and after the peer reviewed paper has been accepted for publication.

Conclusions

The study is feasible in principle. Compatible data are readily available for a mortality study of external radiation workers, although consents and permissions would be required for the BNFL workers. Given the validated urinalysis database for the French workers with consents and permissions for the BNFL workers, the mortality analyses of the 15,000 plutonium and 25,000 uranium workers could start.

4.3 Productions

Deliverables

Binks K and Samson E. Outline Research Study Protocol and protocol on generation of organ specific doses. Final Technical Report: deliverable D4.5, Alpha Risk, Project Number 516483, 2009.

Binks K and Samson E. The Pilot Study Report on the Availability and Extent of Epidemiological Data for the Pierrelatte Plant Workers. Deliverable Report D4.2 Alpha Risk, Project Number 516483, 2008.

Binks K and Scott L D4.3 A protocol on transformation of BNFL worker smoking information for use in epidemiology studies. Deliverable Report D4.3 Alpha Risk, Project Number 516483, 2008.

Riddell T. Internal dosimetry protocol for Alpha Risk project, Work-package 4. Deliverable Report D4.4 Alpha Risk, Project Number 516483, 2008.

Scientific Presentations

This being a feasibility study does not lend itself well to scientific publications. However, many presentations have been given to stakeholders to get to this stage with the Research Study Protocol and consents from French nuclear workers.

Scientific Publications

Samson E, Guseva Canu I, Acker A, Laurier D, Tirmarche M. Tracy U: The French cohort of uranium cycle workers. 10th International Conference on the Health Effects of Incorporated Radionuclides, Santa Fe, USA. 10-14/05/2009.

4.4 References

Binks K and Samson E. Outline Research Study Protocol and protocol on generation of organ specific doses. Final Technical Report: deliverable D4.5, Alpha Risk, Project Number 516483, 2009.

Binks K and Samson E. The Pilot Study Report on the Availability and Extent of Epidemiological Data for the Pierrelatte Plant Workers. Deliverable Report D4.2 Alpha Risk, Project Number 516483, 2008.

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Riddell T. Internal dosimetry protocol for Alpha Risk project, Work-package 4. Deliverable Report D4.4 Alpha Risk, Project Number 516483, 2008.

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Work package 5: Organ dose

Work package leader: **USALZ, W. Hofmann**

5.1 Context and WP objectives

The establishment of a reliable dose-effect relationship requires the calculation of lung doses for the specific exposure conditions reported in epidemiological studies (WP1) for radon, radon progeny, uranium dust and cigarette smoke inhalation, using different computational models. This allows us to analyse the effect of different modelling approaches on resulting doses and to assess the relative magnitude of each exposure pathway and potential correlations among them. This information is important for WP6 in order to compare risk in homes and in mines.

Dosimetry models usually refer to standardised individuals, thus neglecting intersubject variations in morphometry, physiology and biokinetics. Such variations, however, have to be considered, together with fluctuations in the exposure levels, for the analysis of epidemiological data to relate the tumour observed in a given individual to the individual doses incurred and not to an average dose in a larger group.

Since doses to the lungs and to other relevant organs are determined by appropriate biokinetic and dosimetric models, resulting doses depend on the assumptions used in a given model. Such information is important for the uncertainty analysis in exposure levels in epidemiological studies (WP1). Since dose-exposure conversion factors derived in ICRP Publication 65 (ICRP, 1993b) are currently consistently lower than those based on the ICRP (1994) Human Respiratory Tract Model (HRTM), it is absolutely necessary to explore the reasons for such a discrepancy.

Thus the objectives of WP5 are: (i) to calculate estimates of individual absorbed doses to specific target tissues (lung regions, red bone marrow (RBM), kidney, liver) and associated uncertainties in relation to characteristics of individuals (attained age, smoking habits) for the epidemiological studies included in WP1, (ii) to quantify all uncertainties affecting these doses, and (iii) to select the “best” models by comparing different modelling approaches.

5.2 Scientific results

5.2.1. Organ dosimetry for radon progeny, radon gas, and long-lived radionuclides

Doses from inhaled radon and its progeny

The absorbed doses to organs arising from exposure to radon progeny have been calculated by implementing the HRTM, the ICRP Publication 30 Gastrointestinal Tract (GI) model (ICRP, 1979), the ICRP Publication 67 (ICRP, 1993) biokinetic

models for polonium and lead, and the ICRP Publication 30 (ICRP, 1980) biokinetic model for bismuth. A full description of the HRTM is given in ICRP Publication 66 (ICRP, 1994). Briefly, the thoracic airways are divided into three regions: (i) the bronchial region (BB) consisting of the trachea and airway generations 1-8, (ii) the bronchiolar region (bb) consisting of the bronchioles, terminal bronchioles and the respiratory bronchioles (airway generations 9-18), and (iii) the alveolar-interstitial region (AI), comprising the whole gas exchange region.

For the intakes of isotopes of polonium and bismuth, ICRP assumes that the kinetics of the decay products formed within the body are the same as those of the parent, which is referred to as shared kinetics. However, for intakes of isotopes of lead, ICRP assumes that the decay products formed within the body have their own specific biokinetic models, so-called independent kinetics. While HPA have assumed shared kinetics in their calculations for simplicity, BfS have assumed independent kinetics for these radionuclides. Shared and independent kinetics produce very similar doses for radon progeny inhalation in RBM and liver, but doses to the kidney based on independent kinetics are about a factor 2 higher than for shared kinetics.

The organ doses arising from the inhalation of radon gas alone have been evaluated with the dose coefficients calculated by Khursheed (2000), who implemented a dynamic pharmacokinetic model that uses tissue-blood partition coefficients for radon gas in defined organs. While the annual absorbed dose per WLM in the lungs is negligibly small compared to the radon progeny contribution (about 1%), doses are comparable in red bone marrow, kidney and liver. The annual absorbed organ doses arising from the inhalation of radon and its progeny for a Job Type 2 miner (wet drilling + medium ventilation) are listed in Table 1.

Table WP5.1: *Annual absorbed organ dose per WLM arising from exposure to radon gas and its progeny for Job Type 2. The breathing rate is assumed to be 1.2 m^3 h^{-1}.*

Target region/tissue	Absorbed dose (mGy/WLM)		
	Radon progeny		Radon gas
	Shared kinetics	Independent kinetics	
BB basal cells (D_{bas})	4.6	4.6	0.05
BB secretory cell (D_{sec})	9.8	9.8	0.05
BB D_{BB} = 0.5 D_{bas} + 0.5 D_{sec}	7.2	7.2	0.05
bb	7.3	7.3	0.05
AI	0.4	0.4	0.05
RBM	0.0027	0.0023	0.029
Kidney	0.014	0.027	0.0021
Liver	0.0036	0.0032	0.0040

Doses from long-lived radionuclides

Exposure of long-lived radionuclides (LLR), contained in uranium ore dust, have been measured in mines in terms of gross alpha activity (h Bq m^{-3}). Organ doses have been calculated for the following nuclides in secular equilibrium:

^{238}U, ^{234}U, ^{230}Th, ^{226}Ra, ^{210}Pb and ^{210}Po of the ^{238}U chain,
^{235}U, ^{231}Pa and ^{227}Ac of the ^{235}U chain, and
^{232}Th, ^{228}Ra, ^{228}Th and ^{224}Ra of the ^{232}Th chain.

For the long-lived radionuclides (LLR), the ICRP Publication 67 (ICRP, 1993) biokinetic models for polonium, lead, and radium, the ICRP Publication 69 (ICRP,

1995a) biokinetic models for uranium and thorium, and the ICRP Publication 30 (ICRP, 1981) model for actinium and protactinium have been implemented. For lead, radium, thorium and uranium isotopes again dose calculations were again performed with the assumptions of shared kinetics (HPA) and of independent daughter kinetics (BfS) as defined by ICRP (ICRP, 1993, 1995a). For the calculation of independent kinetics the approach (2) defined in Annex C.3 of ICRP Publication 71 (ICRP, 1995b) was used by BfS. This approach may be used in forthcoming ICRP Publications on occupational intake of radionuclides. Some organ doses may differ by up to 20% as compared to those calculated with approach (1) (ICRP, 1995b).

Table 2 lists the cumulative absorbed organ doses over 50 years per unit exposure to LLR for both shared and independent kinetics. The assumption of shared kinetics as opposed to independent kinetics only results in about 10% differences in the cumulative absorbed doses to RBM, liver and kidney.

Table WP5.2: *Cumulative absorbed organ doses over 50 years per unit exposure arising from exposure to long-lived radionuclides. The assumed breathing rate and activity median aerodynamic diameter were 1.2 m^3 h^{-1} and 7 µm, respectively. The doses have been calculated for an activity ratio $^{232}Th/^{238}U = 0.04$.*

Target region/tissue	Cumulative absorbed dose (mGy / h kBq m^{-3}) HPA[a]	BfS[b]	Relative difference (%) BfS-HPA/HPA
BB basal cells (D_{bas})	0.22	0.22	2.6
BB secretory cells (D_{sec})	1.39	1.41	1.7
BB $D_{BB} = 0.5\ D_{bas} + 0.5\ D_{sec}$	0.80	0.82	1.8
bb	0.73	0.74	1.7
AI	0.76	0.77	1.6
RBM	0.32	0.29	- 11.2
Kidney	0.11	0.10	- 6.7
Liver	0.26	0.24	- 9.0

[a] Doses calculated assuming shared kinetics except for ^{226}Ra.
[b] Doses calculated assuming independent kinetics

The *Alphaminer* software program has been developed by HPA to calculate doses to regions of lung, RBM, liver and kidney of each individual miner, based on his specific exposure history. This program reads the input data of the cohort databases (Czech, French and German miners) and calculates the annual absorbed doses from the first year of employment as a miner up to the year 1999. The doses arising from exposure to radon progeny, radon gas, and to the long-lived radionuclides are calculated. The external gamma dose has also been measured and is included in the calculation of the total absorbed dose to specific organs.

For the calculation of RBM dose due to radon gas, radon progeny, LLR and external gamma three models were used: the AlphaMiner software, and two models LT, MM) based on the method proposed by Jacobi and Roth (1995). The total RBM dose by MM and LT for defined exposure conditions are about 20% and 10%, respectively, higher than predicted by AlphaMiner, caused primarily by the higher contributions from radon progeny and LLR, while the radon gas contributions were significantly smaller.

Dose calculations for miners exposed to radon, radon progeny, long-lived radionuclides and external gamma

As an example of the output produced by the Alphaminer software, the annual absorbed dose to the bronchial basal cell region (BB_{bas}) of the lung and to the RBM has been calculated for miner G101 from the German Cohort. This individual worked as a miner between 1956 and 1989. During that time wet drilling was carried out in the mine. Between 1956 and 1966 the ventilation was classified as medium and after 1966 the ventilation was good. After 1972 diesel machinery was used in the mine. For each year between 1956 and 1989 the equilibrium factor, the annual radon progeny exposure, the annual gross alpha activity exposure and the annual gamma dose are all given for this miner in the database. The annual radon progeny exposure ranged from 1.5 to 80 WLM. The annual gross alpha activity exposure (LLR) ranged from 0.02 to 4 h kBq m^{-3} with a mean of 0.8 h kBq m^{-3} and the annual gamma dose ranged from 3 to 32 mGy. Resulting annual absorbed doses for BB_{bas} and RBM are given in Figures 3 and 4, respectively. While the dose to the BB_{bas} is dominated by the radon progeny, the dose to the RBM is dominated by the gamma dose.

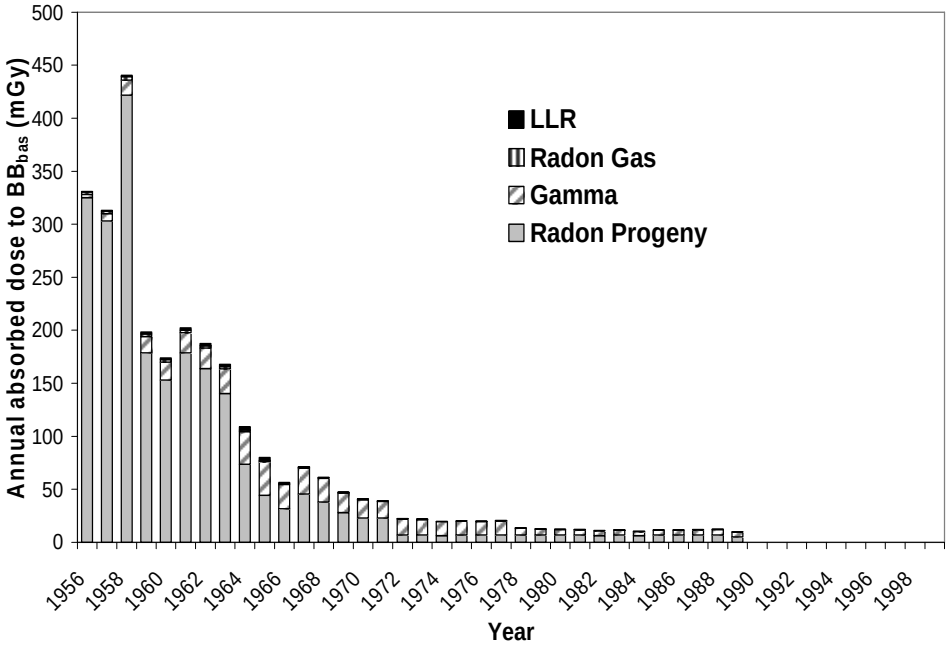

Fig. WP5.1: *Annual absorbed dose to BB_{bas} for miner G101 from the German cohort arising from exposure to LLR, radon gas, radon progeny and external gamma.*

5.2.2. Comparison of radon lung dosimetry models

In order to investigate the degree of dose uncertainty produced by different models, three dosimetry models were compared with each other, representing different classes of models: (i) the ICRP Publication 66 Human Respiratory Tract Model (HRTM) (ICRP, 1994), a deterministic, regional compartment model; (ii) the RADOS model, a deterministic, symmetric airway generation model; and (iii) the IDEAL-DOSE model, a stochastic, asymmetric airway generation model. While all three models are based on the same physical and physiological mechanisms and parameter values, there are significant differences in their model structure. Resulting dose-exposure conversion factors ranged from 7.8 mSv/WLM for IDEAL-DOSE to

11.8 mSv/WLM for HRTM, with 8.3 mSv/WLM for RADOS as an intermediate value (Table 3). Despite methodological and computational differences between the three

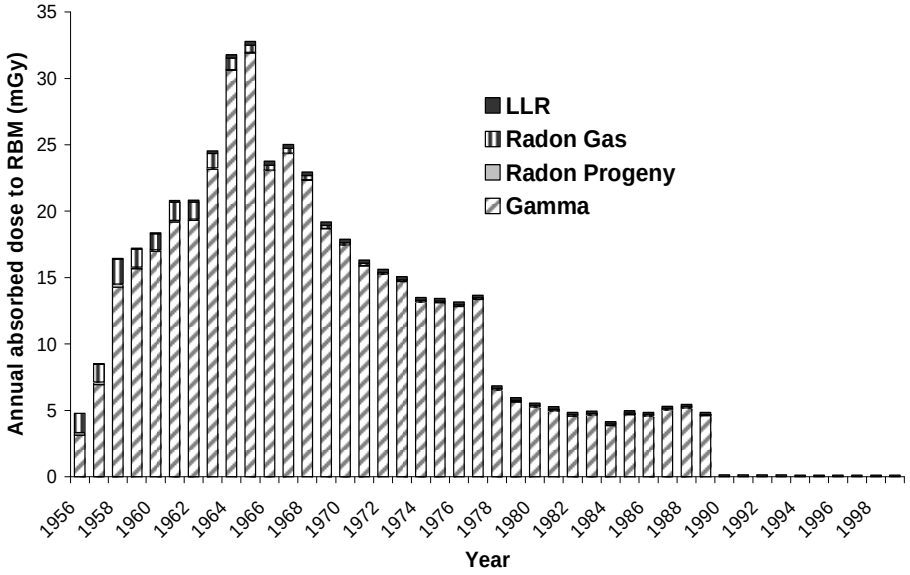

Fig. WP5.2: *Annual absorbed dose to RBM for miner G101 from the German cohort arising from exposure to LLR, radon gas, radon progeny and external gamma.*

models, resulting dose-conversion factors did not appreciably differ from each other, although predictions by the two airway generation models are consistently smaller than that for the HRTM. In conclusion, no major uncertainties will be introduced into the estimation of lung doses by using any of the three models, considering the significant uncertainties in the retrospective assessment of uranium miner exposures and related lung cancer risk.

Table WP.3: *Comparison of effective doses arising from the exposure of 1 WLM for a reference worker predicted by the three models.*

Mode (mSv/WLM)	Effective dose per WLM		
	HRTM	RADOS	IDEAL-DOSE
Unattached	81.1	72.4	64.6[a]
Attached	11.1	7.7	8.3[a]
0.01 unattached + 0.99 attached	11.8	8.3	8.9[a] (7.8)[b]

[a] Arithmetic mean of the lognormal dose-distribution; [b] Geometric mean (median) of the lognormal dose-distribution

5.2.4. Lung dosimetry for radon progeny in smokers

Cigarette smoking may change the morphological and physiological parameters of the human lung. Thus the primary objective of this analysis was to investigate to what extent these smoke-induced changes can modify deposition, clearance and resulting doses of inhaled radon progeny relative to healthy nonsmokers. Doses to sensitive bronchial target cells were computed for four categories of smokers: (i) light, short-term smokers; (ii) light, long-term smokers; (iii) heavy, short-term smokers; and (iv) heavy, long-term smokers (see Table 4). Because of apparent inconsistencies of the reported physiological changes, smoker categories were further subdivided into

smoker 1 (smaller mucus thickness and slower mucus velocity) and smoker 2 (larger mucus thickness and faster mucus clearance). Doses were computed with the stochastic lung dosimetry code IDEAL-DOSE (Winkler-Heil et al., 2007). Because of only small changes of morphological and physiological parameters, doses for the light, short-term smokers hardly differed from those for nonsmokers. For light, long-term smokers and heavy, short-term smokers, even a protective effect could be observed for certain parameter assumptions, caused by a thicker mucus layer and increased mucus velocities. Only in the case of heavy, long-term smokers were doses higher by about a factor of two than those for nonsmokers, caused primarily by impaired mucociliary clearance, higher breathing frequency, reduced lung volume and airway obstructions. These higher doses suggest that the contribution of inhaled radon progeny to lung cancer risk in smokers may be higher than currently assumed on the basis of nonsmokers (Baias et al., 2009). This further implies that lung cancer cases observed for a given exposure category, may be shifted to higher exposure categories in the case of heavy, long-term smokers, if based on the dose-exposure conversion factor for nonsmokers.

Table WP5.4: Dose-exposure conversion factors for a nonsmoker and four smoker categories: Light, short-term smoker; light, long-term smoker; heavy, short-term smoker; and heavy, long-term smoker.

Smoker category		Effective dose (mSv/WLM)
Nonsmoker		7.20
Light, short-term smoker:	smoker 1	7.25
	smoker 2	7.17
Light, long-term smoker:	smoker 1	6.40
	smoker 2	1.74
Heavy, short-term smoker:	smoker 1	6.40
	smoker 2	1.74
Heavy, long-term smoker		13.34

5.2.5. Dose-exposure conversion factors in homes and mines

K-factors are used to estimate lung cancer risk per unit exposure (in WLM) to radon progeny in homes from the observed risk to miners per unit exposure (in WLM) in mines on the assumption that the risk of excess lung cancer is directly proportional to the equivalent dose to the lung. Thus, the K-factor is defined as the ratio of the equivalent dose to the lung per unit exposure in homes to that in mines. In the present study, dose-conversion factors for mines and homes and resulting K-factors were predicted by both the HRTM and the IDEAL-DOSE model. Dose-exposure conversion factors were calculated for different exposure conditions, physical activity patterns, gender and subject age. Related K-factors ranged from 0.8 to 1.3, consistent with previously reported K-factor values (Table 5). The results of our calculations indicate that the selection of aerosol parameters and physical activity patterns are the major determinants of the K-factors. If aerosol parameters and physical activity patterns are known for specific populations, then K-factors should be derived for these exposure scenarios. If not, it may be prudent to assume, for radiation protection purposes, that dose-conversion factors are practically the same in both home and mine exposure conditions as all values are centered around 1.

Table WP5.5: *Comparison of K-factors obtained for different physical activities and exposure conditions.*

Modelling approaches	K-factor
Marsh et al. (2005) (different exposure conditions, gender and age)	0.7 – 1.1
Hofmann and Winkler-Heil (2009)* (different physical activities)	0.8 – 1.3
Hofmann and Winkler-Heil (2009)* (typical exposure conditions and physical activities)	0.8

*see deliverable D5.7

2.5.6. Intersubject variability of radon progeny doses in the lungs

Intersubject variability of bronchial doses is defined in this study as the effect of morphological and physiological parameter variations among a group of subjects on bronchial doses for defined exposure conditions, where each subject is characterized by a dose distribution (intrasubject variability). In contrast, each individual is characterized by a single dose value if deterministic dose models are applied. Thus, by definition, stochastic intersubject variations of bronchial doses will produce wider intersubject dose distributions than the commonly used deterministic models, such as the HRTM (see the analysis of exposure uncertainty below).

The main sources of intersubject variations considered in the present study were: (i) size and structure of nasal and oral passages; (ii) size and asymmetric branching of the human bronchial airway system, leading to variations of diameters, lengths, branching angles, etc.; (iii) respiratory parameters; (iv) mucociliary clearance rates; and, (v) thickness of the bronchial epithelium and depth of target cells. For the calculation of deposition fractions, retained surface activities and bronchial doses, parameter values were randomly selected by Monte Carlo methods from their corresponding probability density functions, derived from experimental data. Bronchial doses, expressed in mGy/WLM, were computed for specific mining conditions, i.e. for defined size distributions, unattached fractions and physical activities. Resulting bronchial dose distributions could be approximated by lognormal distributions (Fig. 3). Geometric standard deviations illustrating intersubject variations ranged from about 2.3 in the BB region to 4.7 in the bb region. The major sources of the intersubject variability of bronchial doses for inhaled radon progeny are the asymmetry and variability of the linear airway dimensions, the filtering efficiency of the nasal passages and the thickness of the bronchial epithelium, while fluctuations of the respiratory parameters and mucociliary clearance rates seem to compensate each other.

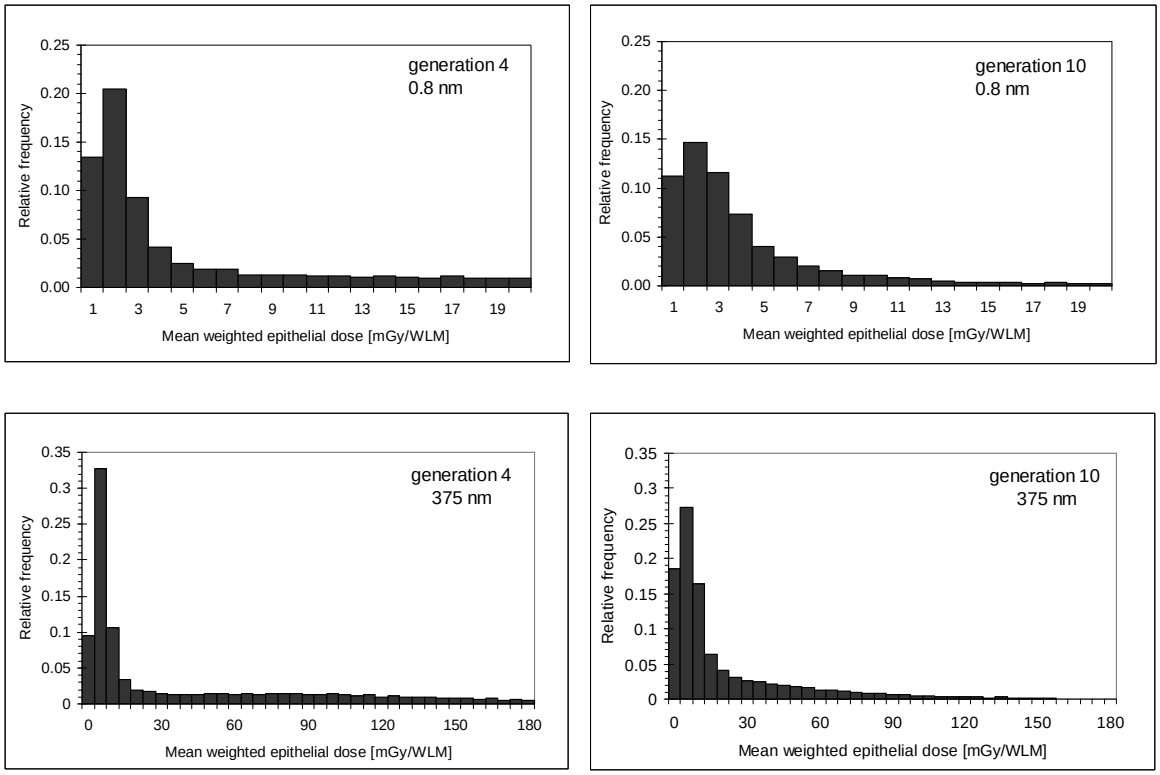

Fig. WP5.3: *Probability distributions of weighted absorbed doses, produced by ^{218}Po and ^{214}Po alpha particles, for 0.8 nm (unattached fraction) and 375 nm (attached fraction) unit density particles in bronchial airway generation 4 and bronchiolar airway generation10 for defined uranium miner exposure conditions.*

5.2.7. Analysis of exposure uncertainty in radon studies

The relatively large dose to the lungs mainly arises from the exposure to radon progeny. A parameter analysis has been performed to derive the frequency distribution of the absorbed dose to regions of the lung per unit exposure to radon progeny (Marsh and Birchall, 2009) . The analysis was performed using the HRTM, assuming that the HRTM is a realistic representation of the physical and biological processes, and that the parameter values are uncertain. The parameter probability distributions used in the analysis were based upon measured data published in the open literature. Parameters considered include: (i) aerosol parameters, such as size distribution; (ii) subject related parameters, such as breathing rate and fraction breathed through the nose; (iii) target cell parameters, such as depth of basal and secretory cell layer; and (iv) absorption rates of attached and unattached radon progeny. Calculations were performed for two exposure scenarios: (i) wet drilling + medium ventilation, and (ii) wet drilling + good ventilation + diesel engines.

The frequency distributions of the lung regional absorbed doses per WLM can be approximated by lognormal distributions, characterized by geometric mean (median) and geometric standard deviation (GSD) (Table 6).

The uncertainties for different parameters were classified by shared (uncertainties are 100% correlated between subjects), unshared (no correlation between subjects), and mixed (combination of shared and unshared) errors. The unshared errors contributed the most to the overall uncertainty. The uncertainty in the absorbed dose to each lung region arising from the uncertainty in the aerosol parameter values alone could also be approximated by a lognormal distributions with a GSD of about 1.3 (Marsh and Birchall, 2009). This GSD is relatively small compared with the corresponding values calculated for inter-subject variability, indicating that the overall uncertainty is dominated by inter-subject variability.

Table WP5.6: *Lung regional absorbed doses per WLM characterised by median (geometric mean) and geometric standard deviation (GSD). Exposure conditions assumed are: (A) Wet drilling + medium ventilation, and (B) wet drilling + good ventilation +diesel engines. Lung regions considered are: bronchial basal cells (BB_{bas}), bronchial secretory cells (BB_{sec}), bronchiolar (bb), and alveolar interstitial (AI) regions.*

Target region/tissue	Exposure conditions A		Exposure conditions B	
	Median (mGy/WLM)	GSD	Median (mGy/WLM)	GSD
BB_{bas}	5.9	1.6	3.9	1.6
BB_{sec}	11.7	1.7	7.7	1.7
Bb	8.0	1.4	6.6	1.4
AI	0.4	1.3	0.3	1.4

One of the objectives of WP5 was to compare different dosimetry models to investigate whether the corresponding doses differ from each other, and if so, which are the factors causing these differences. Such comparisons included two lung dosimetry models for inhaled radon progeny (HRTM vs. IDEAL-DOSE) and two organ dosimetry models for inhaled radon progeny and LLR (independent vs. shared kinetics). In both cases, resulting doses did not appreciably differ from each other, suggesting that the use of a specific model will hardly affect the dose calculations for miners.

5.3 Productions

Deliverables

- D5.1 Interim report on dose models and exposure uncertainty
- D5.2 Analysis of exposure uncertainty in radon studies
- D5.3 Inter-subject variability in lung dosimetry
- D5.4 Lung dosimetry models for radon progeny inhalation
- D5.5 Lung dosimetry model for uranium dust inhalation
- D5.6 Organ dosimetry for radon progeny and long-lived radionuclides
- D5.7 Assessment of exposure conversion factors for radon exposures in mines and homes
- D5.8 Analysis of dose uncertainty: comparison of different dosimetry models
- D5.9 Final analysis of dose calculations and risk assessment for dose-response modeling
- D5.10 Final report

Scientific presentations

Tomasek L., Malátová, I.: Leukemia and lymphoma among Czech uranium miners. III. International Symposium on Chronic Radiation Exposure: Biological and Health Effects, October 24-26, 2005, Chelyabinsk, Russia.

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Hofmann, W., Fakir, H., Pihet, P.: Internal microdosimetry of inhaled radon progeny in bronchial airways: advantages and limitations. Workshop on Internal Dosimetry of Radionuclides, October 2-5, 2006, Montpellier, France

Marsh, J.W., Bessa, Y., Birchall, A., Blanchardon, E., Hofmann, W., Nosske, D., Tomasek, L.: Dosimetric models used in the Alpha-Risk project to quantify exposure to uranium miners to radon gas and its progeny. 5th Conference on Protection Against Radon at Home and at Work, September 9-15, 2007, Prague, Czech Republic.

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Hofmann, W., Winkler-Heil, R., Hussain, M.: Modelling intersubject variability of bronchial doses for inhaled radon progeny. 10th International Conference on Internally Deposited Radionuclides, May 10-14, 2009, Santa Fe, NM, USA.

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Work Package 6: Integration of results

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6.1 Context and WP objectives

Estimates of lifetime lung cancer risks following exposure to radon in homes are generally based on studies of miners. However, recent strong and supportive findings from combined analyses of case-control studies have shown that residential radon exposure is associated with an increased risk of lung cancer (Darby et al. 2005, 2006; Krewski et al. 2005, 2006; Lubin et al. 2004). However, there are differences between the environment in homes and miners, as well as differences in smoking levels and in the ability to adjust for smoking between these studies. Miners and the general population also differ with respect to age, gender and the range and period of exposures. Improving the quantification and understanding of lung cancer risks from radon is an important issue, which needs to be addressed in the management of radon exposure.

The general and specific objectives for Work Package 6 are:

- To integrate findings from studies of lung cancer following residential and occupational radon exposures, based on:
  - 3 European case-control studies of uranium miners in France, Germany and the Czech-Republic (Alpha-Risk: WP1),
  - Findings from 11 cohort studies of radon-exposed miners (in China, Canada, Europe, USA and Australia), including some studies with smoking information (BEIR VI 1999),
  - The combined analysis of 13 European residential case-control studies from nine countries: Austria, the Czech-Republic, Finland (2 studies), France, Germany (2 studies), Italy, Spain, Sweden (3 studies), and United Kingdom (Darby et al. 2005, 2006).
- To develop a model from the case-control analysis of European uranium miners and to compare lung cancer risk estimates from this analysis with those based on the BEIR VI (1999) pooled analysis of cohort studies of radon-exposed miners and the combined analysis of 13 European residential radon case-control studies (Darby et al. 2005, 2006). In so doing, consideration is given to the modifying effects of age, smoking and time since exposure. To assist with the latter comparison, the link between the exposure measures normally used in studies of uranium miners and of people exposed to radon in homes is also addressed.
- To calculate lifetime lung cancer risks associated with radon exposure, based on various models and exposure scenarios (eg. concerning the impact of radon mitigation of homes). This involves using appropriate software to calculate lifetime risks estimates for individuals, comparing results between miner and residential models and assessing the impact of smoking.

6.2 Scientific results

6.2.1. Comparison of lung cancer risk estimates from European studies of occupational and residential radon exposure

The aim in this work is to develop a model of lung cancer risk due to radon exposure, by comparing the occupational and residential radon results. In so doing, it is important to understand how radon risk estimates vary with modifying factors between occupational and residential studies, particularly age, smoking and time since exposure. Hence, this work involves an analysis of the combined data from a new case-control analysis of uranium miners from 3 European studies (in the Czech Republic, France and Germany) and comparison of lung cancer risk estimates from this analysis with:

- the BEIR VI (1999) pooled analysis of cohort studies of radon-exposed miners, which includes some cohorts with smoking information, and
- a combined analysis of 13 European residential radon case/control studies (Darby et al. 2005, 2006).

To assist with the latter comparison, the link between the exposure measures normally used in studies of uranium miners and of people exposed to radon in homes is also addressed.

Analysis of data from three European case-control studies of uranium miners

Three European case-control studies nested within the French, Czech Republic and German cohorts of uranium miners were conducted under WP1 of Alpha-risk and are described in detail elsewhere. A total of 1,476 miner workers with lung cancer and 3,389 controls were included in the analysis. Radon exposures were expressed in Working Level Months (WLM) and have been aggregated over the full period up to 5 years previously or split into time since exposure 'windows'. The analyses are restricted to the 1,046 (71% of the) lung cancer cases and 2,492 (74% of the) controls for whom smoking histories are available. All subsequent analyses use the following four smoking stratification: never smoker, ex-smoker who had stopped smoking 10 years or more (≥ 10) previously, ex-smoker who had stopped smoking within the last 10 years (<10), or current smoker at the index date.

On the basis of a linear excess relative risk model, the overall ERR (excess relative risk) estimate was 1.02 (95% CI: 0.60-1.75) per 100 WLM without adjustment for smoking, whereas with such an adjustment the ERR estimate was slightly reduced to 0.80 (95% CI: 0.44 -1.43) per 100 WLM. Most of the lung cancer cases arose in the Czech data (672, 64%), compared to the German (314, 30%) and the French (60, 6%) data. The ERR/WLM varied to a statistically significantly degree between studies (P=0.02). Since these differences between studies may be explained by the effect of exposure rate, analyses were also conducted using data restricted to cumulative exposures below 1000 WLM (cases=953; controls=2375); when this was done, the differences in the ERR/WLM across studies were no longer statistically significant (P=0.37).

When study participants were subdivided according to five categories of mean cumulative radon exposure, as shown in Figure WP6.1, the risk was linearly related to cumulative radon exposure, except for the highest exposure group (Fig. WP6.1a). This flattening of the exposure-response trend at very high exposures (Fig.WP6.1a) may reflect cell killing at high doses and a such response curve has also seen in other studies of radiation damage at high doses (ICRP 2007, UNSCEAR 2008).

Deviations from the linear model were evaluated using both a linear-quadratic (LQ) model and a linear-exponential (LE) exposure-response model and both the LQ (P<0.001) and the LE (P<0.001) models provided a statistically significant better fit than the linear model. When the data were restricted to exposures below 1000 WLM, the trend in the relative risk appeared to be consistent with linearity (Fig.WP6.1b), but the LQ (P=0.03) and the LE (P=0.02) models still provided a significantly better fit than the linear model. When the data were limited to cumulative exposures under 300 WLM, neither the LQ (P=0.10) nor the LE (P=0.10) model statistically significantly improved the fit compared to the linear model. Consequently, later analyses considered, *inter alia*, data restricted to <300 WLM.

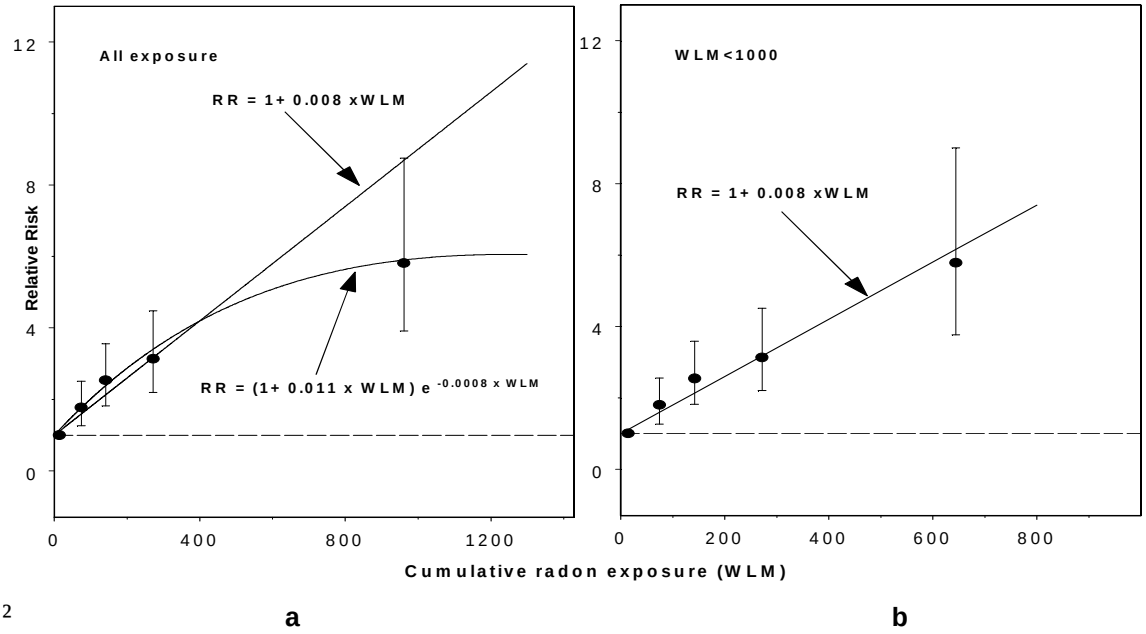

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Fig. WP6.1: *Relative risks of lung cancer in relation to cumulative radon exposure, having adjusted for smoking status, for the combined European miner case-control data. The relative risk and 95% confidence interval are shown for various categories, together with trend estimates based on linear and nonlinear (LE) models. The dashed line represents an RR of 1. Fig 1(a) covers all exposures, whereas Fig 1(b) is based on data for exposures below 1000 WLM.*

With the data restricted to cumulative exposures less than 300 WLM, no statistically significant differences in the ERR per WLM between countries were observed. The ERR per WLM decreased with increasing attained age and was greater for exposures within the past 25 years than for exposures received earlier, but was not affected significantly by exposure rate. Although the ERR/WLM was larger for ex-smokers and never-smokers than for current smokers, these differences were not statistically significant.

The findings from the combined analysis of the combined European miner cohort data, obtained in WP1, differ from those presented here based on the combined European miner case-control data. This is because the present analysis was based on 1046 cases and their controls with smoking information and included an adjustment for the effect of smoking, whereas the cohort analysis included 1538 cases but had no smoking adjustment. As a consequence of the smaller number of cases, the case-control analysis might have limited statistical power to detect

modifying effects such as exposure rate in comparison to the cohort analysis. On the other hand, the case-control analysis is less susceptible to confounding by smoking.

Comparison of findings from the joint analysis of three European uranium miner studies and BEIR VI estimates

The exposure-age-concentration (EAC) model was fitted to the combined European miner case-control data using the same parameterisation as that used by the BEIR VI Committee (BEIR VI 1999). The patterns of risk with radon exposure from the combined European miner analysis, both with the unrestricted data and with data restricted to exposures less than 1000 WLM or less than 300 WLM, were generally consistent with those reported by BEIR VI (1999). The following conclusions can be drawn by applying the BEIR VI EAC model to the European miner data and from analysis of the radon and smoking interaction:

- The findings from the European miner studies support the BEIR VI findings that the ERR per 100 WLM decreases significantly with increasing time since exposure.
- Age at risk (ie. attained age) and exposure rate do not improve the fit of the EAC model to the European miner data, but the BEIR VI parameter estimates for the effect of attained age lie within the confidence intervals of the corresponding estimates from the fit to the European miner data. The estimates from exposure rate are not consistent with BEIR VI estimates.
- *Radon and smoking*: The estimate of the ERR per 100 WLM for never-smokers from analysis of the unrestricted European miner data is 1.01 (95% CI: 0.25-3.95), which is similar to the BEIR VI estimate based on 6 studies of cohort miners for which smoking information was available (1.02; 95% CI: 0.15-7.80). The ERR/100 WLM based on the unrestricted combined European miner data for current smokers is 0.56 (95% CI: 0.27-1.10), whilst the ERR/100 WLM for ever smokers of 0.77 (95% CI: 0.41-1.40) is consistent with the BEIR VI estimate for ever-smokers (0.48; 95% CI: 0.18-1.27). The results are consistent with a sub-multiplicative interaction effect, although there was no statistically significant variation in the ERR/WLM between smoking categories in either the European or the BEIR analysis.

Equating the units of exposure from miners and residential studies

The unit of measurement used for residential radon studies is Bq/m^3, corresponding to the radon gas concentration, whereas for studies of miners the unit of measurement is Working Level Month (WLM), representing cumulative exposure. Hence, in order to compare the results from the European miner data with the results from the European residential analysis, conversion procedures were applied to risk estimates for miners, assuming 10, 20 or 30 years' exposure in homes at a concentration of 100 Bq/m^3 and assuming 7000 hours spent at home per year. The conclusions based on various analyses of the restricted and unrestricted miner data are as follows:

- For 10 years exposure, the ERR/WLM ranges from 0.011 to 0.032 across the various analyses and the corresponding value for the ERR at 100 Bq m^{-3} ranges between 0.05 and 0.14.
- For 20 years exposure, the ERR/WLM ranges over 0.018-0.051 and the corresponding ERR/100 Bq m^{-3} is in the range 0.16-0.45.
- For 30 years exposure, the ERR/WLM ranges over 0.007-0.085 and the corresponding ERR/100 Bq m^{-3} is in the range 0.09-1.12.

In each of the above, the largest value arises for the analysis restricted to exposures below 50 WLM which involves limited numbers of cases and controls; the estimates from most of the other analyses are towards the lower end of the relevant range.

Comparison of findings from the joint analyses of three European uranium miner studies and 13 European residential radon studies

The results from the European miner data based on conversions to time weighted averaged radon concentration (expressed per 100 Bq m^{-3}) were compared with those from the joint analysis of 13 European residential radon studies (Darby et al. 2005, 2006). The following values are based on the miner data limited to cumulative exposures of less than 300 WLM and on the exposure window 5-34 years prior to the index date. The main conclusions from this comparison are as follows:

- *Overall ERR estimate:* The ERR per 100 Bq m^{-3} from the miners analysis, namely 0.21 (95% CI: 0.10-0.38), is in line with findings for the overall value from the residential analysis, ie. 0.16 (95% CI: 0.05-0.31), as well as with the value from the residential analysis that is specific to males, ie. 0.25 (95% CI: 0.09-0.49) (Darby et al. 2006).
- *Age at risk*: In the combined European miner data, the ERR declines with increasing attained age and this variation approaches statistical significance (P=0.09). In contrast, in the European residential studies, there is no evidence of the ERR differing according to age (P=0.26). Although the age-specific estimates of ERR per 100 Bq m^{-3} from the European residential analysis tend to be lower than the corresponding miner-based estimates, the associated confidence intervals overlap.
- *Joint effects of radon and smoking*: In both the European miner and residential analyses, there is no statistically significant difference in the ERR between smoking categories. However, in both analyses the ERR per 100 Bq m^{-3} was higher (by about a factor of two) among never-smokers than among current smokers, although these differences were not statistically significant. Whilst the magnitude of the relative risks differed between the miner and residential analyses, the overall patterns in risk were generally similar in both cases. In particular, the absolute risk of lung cancer due to radon exposure was substantially greater among current smokers than among never-smokers, even based on a sub-multiplicative model for the joint effect of radon and smoking fitted to the miner data.
- *Exposure time windows*: In the European residential studies, the coverage of exposure period by measurements was higher in the more recent past than in the more distant past, whereas in the European miner studies, coverage was higher in the distant past than in the more recent past. The findings differ between the two sets of studies: the ERR decreased with increasing time since exposure – particularly between exposures more than 25 years previously and more recent exposures - in the European miner studies, while in the European residential studies the ERR did not appear to vary with time since exposure. Comparison of the results for specific time exposure windows between the residential and miner data is complicated because residential-based estimates with correction for random uncertainties in radon measurements have not been published.

Proposed models for risk of lung cancer from radon

Consequently, to develop a model of lung cancer risk due to radon exposure, the BEIR VI Exposure-Age-Concentration (EAC) model was modified. The parameters in the model are based on findings from the European miners case-control analysis, restricted to data less then 300 WLM because the exposure-response relationship is linear over this range. The miner data indicate that time since exposure has a major effect, such that the ERR is higher in the recent past (5-14 and 15-24 years earlier) compared to the more distant past (25+ years). Hence, based on a 5 year latency period, radon exposures expressed either as cumulative exposure or time-weighted average concentration in homes are considered with two time windows: those exposures received during the previous 5-24 years (referred to below as $w_{5\text{-}24}$) and those received 25 or more years previously (ie. w_{25+}). Since the European miner analysis found that the dependence of ERR on exposure rate was not statistically significant, the proposed model does not include an effect of exposure rate; the focus here is on application to low exposure rates. In order to allow for the effect of attained age, the ERR is multiplied by an age function, based on the European miner data. This function takes the value 1 at ages less than 55 and at older ages decreases by a factor of 2 for every 10 years of attained age after age 55. 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. Both multiplicative and sub-multiplicative models for the joint effect of radon and smoking on the ERR are considered.

6.2.2. Calculation of lifetime lung cancer risks associated with radon exposure, based on various models and exposure scenarios

In order to derive the lifetime risk for radon exposure induced death from lung cancer, we used a life-table with a baseline lung cancer rates multiplied by the excess relative risks (ERR). Life-table methods account for the effects of competing causes of death, which is necessary because the probability of dying from a radon-induced lung cancer depends on the age-specific rates of death from all causes as well as lung cancer death rates. For the adjustment of age and gender specific lung cancer mortality and all-causes deaths to reflect rates in continuing smokers, ex-smokers & never-smokers, we used the 2004 US census data (Woolshin et al, 2008).

The lifetime risk estimates vary by around a factor of 2 between the various risk models: the European residential model provides the lowest risk estimates, while the BEIR VI-EAC model gives the highest values. The lifetime risk estimates from the the WP6 and WP1 European miner models lie within this range.

Using the WP6 European miner model, Table WP6.1 shows lifetime risk estimates for male continuing smokers, ex-smokers from age 50 and never smokers, based on multiplicative and sub-multiplicative models for the joint effect of radon exposure and smoking. The multiplicative model implies that the ERR is the same for each smoking category. For the sub-multiplicative model, the baseline ERR/WLM has been multiplied by 0.75 for continuing smokers and by 1.5 for never-smokers and no adjustment factor was applied for ex-smokers. As expected, the lifetime risk for radon-related lung cancer was highest for continuing smokers and the lowest for never smokers. Based on a multiplicative model, the lifetime risk of radon induced lung cancer death by age 75 years for a male non-smoker who has lived from age 30 in a home with a radon concentration of 50 Bq m^{-3} (ie. the European long-term average) is estimated to be about 0.08% (Table WP6.1). This rises to 0.34% for a

radon concentration of 200 Bq m^{-3} and further increases to 0.67% and 1.01% for 400 and 600 Bq m^{-3} respectively (Table WP6.1). For a male continuing smoker, the lifetime risk of radon induced lung cancer death by age 75 years who has lived from age 30 in a home with a radon concentration of 50 Bq m^{-3} is estimated to be 1.40% and rises to 5.44% at 200 Bq m^{-3}, 10.5% at 400 Bq m^{-3} and 15.11% at 600 Bq m^{-3}. For a male who quit smoking at age 50 years, the lifetime risk of radon-related lung cancer death is around half of that for a male continuing smoker with the same radon exposure, but this risk is remain considerably higher than that for a male never-smoker (Table WP6.1).

The estimates under a sub-multiplicative model for the joint effects of radon and smoking are slightly smaller for continuing smokers and larger for never-smokers than the corresponding estimates under a multiplicative model. However, under a sub-multiplicative model, the lifetime risk of radon-induced lung cancer is still substantially higher for continuing smokers than for never-smokers.

Table WP6.1: *Estimated risk (%) of radon-induced lung cancer death in <u>males</u> up to age 75 years from age 30 years for continuing smokers, ex-smokers from age 50 and never smokers using the WP6 miner model with and without adjustment for a sub-multiplicative relationship between radon exposure and smoking*

	WP6 miner model					
	Multiplicative [a]			**Sub-multiplicative** [b]		
Radon exposure (Bq m^{-3})	Continuing smoker	Ex-smoker from age 50	Never smoker	Continuing smoker	Ex-smoker from age 50	Never smoker
Males						
25	0.58	0.26	0.03	0.43	0.26	0.05
50	1.40	0.64	0.08	1.06	0.64	0.13
80	2.22	1.02	0.13	1.67	1.02	0.20
100	2.78	1.28	0.17	2.10	1.28	0.25
200	5.44	2.54	0.34	4.13	2.54	0.51
400	10.5	4.99	0.67	8.02	4.99	1.01
600	15.11	7.36	1.01	11.68	7.36	1.51

[a] : The same risk model is applied to smokers and non-smokers without modification;

[b] : Adjusted by multiplying the baseline ERR/WLM by 0.75 for continuing smokers and by 1.5 for never-smokers.

Various exposure scenarios were also considered, assuming (for example) that an individual moves home or radon mitigation is carried out in a home. Table 2 presents lifetime risk of radon-induced lung cancer death in males up to age 75 years, assuming a radon concentration of 400 Bq m^{-3} in that person's home from age 30 onwards (ie. without remediation) or 400 Bq m^{-3} up to age 50, followed by a radon concentration of 100 Bq m^{-3} from age 50 years onwards (ie. with remediation), based on various smoking categories and risk models.

***Table WP6.2**: Estimated risk (%) of radon-induced lung cancer death in <u>males</u> up to age 75 years, based on 400 Bq m^{-3} from age 30 to 50 years and 100 Bq m^{-3} from age 50 years onwards(based on a multiplicative model for the joint effect of smoking and radon)*

	Continuing smoker		**Ex-smoker from age 50**		**Never smoker**	
Risk Model	*Without* [a] *remediation*	*With* [b] *remediation*	*Without* [a] *remediation*	*With* [b] *remediation*	*Without* [a] *remediation*	*With* [b] *remediation*
Residential	5.8	4.1	2.7	1.9	0.39	0.26
BEIR VI	12.5	9.5	6.1	4.6	0.85	0.63
WP1	8.5	5.7	4.2	2.8	0.60	0.40
WP6	10.5	7.7	5.0	3.6	0.67	0.48

[a] : exposed 400 Bq m^{-3} for lifetime up to age 75 years from 30 years

[b] : exposed 400 Bq m^{-3} up to age 49 years and exposed 100 Bq m^{-3} from age 50 years up to age 75 years.

For a continuing smoker living in a home with a radon concentration of 400 Bq m^{-3}, doing nothing translates into an estimated 5.8% lifetime risk of radon-related lung cancer, based on the model derived from the European residential studies. Mitigating for radon while continuing to smoke reduces this lifetime risk by nearly 30%, to 4.1% (Table WP6.2). Quitting smoking but not mitigating for radon decreases the lifetime radon risk by around half, to 2.7%. Combining radon mitigation and quitting smoking reduces the lifetime radon risk by nearly 70%, to 1.9%. Whilst the absolute values for the lifetime risk vary to some degree between risk models, the percentage reductions associated with radon mitigation or stopping smoking do not vary greatly according the model used.

A notable finding from Table WP6.2 is that - for each of continuing smokers, ex-smokers and never-smokers – radon mitigation at age 50 would lower the lifetime risk of radon-induced lung cancer by about one-third. Thus, even for persons in their 50s, radon migration could have a notable impact on their risk of death due to radon exposure.

6.3 Productions

<u>Deliverables</u>

Hunter N, Muirhead C, Leuraud K, Laurier D, Kreuzer M, Schnelzer M, Grosche B, Tomasek L, Bochicchio F, Hofmann W, and Tirmarche M. Definition of a practical work programme 6 (WP6). Alpha-Risk Deliverables D6.1, Alpha-Risk Project (EC FP6, Project no. 516483), March 2007

Hunter N, Muirhead C, Leuraud K, Laurier D, Kreuzer M, Schnelzer M, Grosche B, Tomasek L, Bochicchio F, Hofmann W, and Tirmarche M. Comparison of lung cancer risk estimates from European studies of occupational and residential radon exposure. Alpha-Risk Deliverable D6.2, Alpha-Risk Project (EC FP6, Project no. 516483), October 2009.

Hunter N, Muirhead C, Leuraud K, Laurier D, Kreuzer M, Schnelzer M, Grosche B, Tomasek L, Bochicchio F, Hofmann W, and Tirmarche M. Calculation of lifetime lung cancer risks associated with radon exposure, based on various models and exposure scenarios. Alpha-Risk Deliverable D6.3, Alpha-Risk Project (EC FP6, Project no. 516483), October 2009.

Scientific presentations

Muirhead CR and Hunter N. Lung cancer risk in mines and homes. Presentation at the Alpha-risk Open Meeting – "*Results of a European Research Program on Health Effects from Chronic Exposure to Radioactive Alpha Emitters*" (Paris, 23 October 2009).

Publications

Hunter N et al. Comparison of lung cancer risk estimates from European studies of occupational and residential radon exposure. In preparation.

Hunter N et al. Calculation of lifetime lung cancer risks associated with radon exposure, based on various models and exposure scenarios. In preparation.

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Conclusion and perspectives

Achieved results

The collaborative project "Alpha Risk" conducted within the 6th Framework Programme of the European Community provided new results in three different directions: epidemiology, internal dosimetry and mechanistic modelling in regards to three alpha emitters, radon and its daughters, uranium, and plutonium.

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, WP2 with WP5, and of WP3 with WP4. This collaborative work has allowed studying more thoroughly health effects of radon and other alpha emitters, and notably the modifying factors of these effects. It has also led to very innovative developments in the production of new knowledge, especially regarding the calculation of absorbed doses to different organs and organs' regions. Main specific points are listed below per work package.

Within Work package 1, Uranium miners studies numerous outcomes were obtained:

- A joint database combining the three European cohorts (French, Czech, and German) of uranium miners was created, including individual information on more than 50,000 miners with a mean follow-up duration of more than 26 years.
- The analysis of mortality risk confirmed an excess of lung cancer risk. Excesses or trends with cumulative exposure were also observed for leukaemia, kidney cancer and cerebrovascular diseases, but not confirmed in all three cohorts.
- This large joint database allowed examining in details 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. This is to date the largest dataset allowing considering the effect of both radon exposure and smoking on the risk of lung cancer death among uranium miners.
- 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.

- Biologically-based two stage clonal expansion models were used to analyze 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.
- An important effort was dedicated to the characterization of measurement errors associated to radon exposure. This work has 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.
- A projection method was developed, that appeared as a suitable technique 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.
- We performed the first study to analyse the risk of cancer in relation to organ doses among miners. The collaboration with WP5 dosimetrists allowed calculating individually organ doses associated to chronic exposures to radon gas, radon decay products, external gamma rays and long-lived radionuclides. The Alpha Miner software was developed by WP5 partners specifically for that study. This software allowed estimating absorbed and equivalent doses to lung, kidney, liver and red bone marrow 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 showed a positive and significant dose-risk relationship for lung cancer and for leukaemia.
- A large case-control study of former uranium miners in East Germany (377 cases and 980 controls) allowed to analyse the risk of leukaemia associated to both occupational exposures (radon, gamma rays, long lived radionuclides) and X-ray examinations due to diagnostic examinations. Red bone marrow 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.

Within Work package 2, Indoor radon study, the four main achievements were the following:

- Preparation of the full data set for world pooling of indoor radon and lung cancer case-control studies in uniform format. This data set contains all the data included in the European, North-American and Chinese pooled analyses, and some further data sets. Unfortunately the analysis of the world pooled studies could not be concluded within this project.
- A review of new data sets and published papers on repeated radon measurements in different years in the same dwellings was completed. This review was conducted because: i) studies on year-to-year variations of radon concentration can be used to evaluate radon exposure uncertainty in residential epidemiological studies; ii) risk estimates significantly increase after 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 and new data were analysed grouping the studies carried out in Europe, in China and in North America, and compared with corresponding case-control studies in order to evaluate the

possible impact on corresponding risk estimates. Year-to-year variations of radon concentration were higher in studies conducted in Europe (except Italy) and China, compared to those conducted in North-America. However, in most cases radon concentration measurements carried out in epidemiological studies and in year-to-year variation studies differ for technique and protocol (e.g. detector exposure period). Therefore, for most epidemiological studies the evaluation of radon exposure uncertainty remains affected by a substantial uncertainty.

- A comparison of two different approaches to correct lung cancer risk in residential studies taking into account radon exposure uncertainties. Both approaches, the simpler one and the more sophisticated one, produce very similar point estimates and confidence intervals.
- 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.

Within Work package 3, Nested case-control studies among nuclear workers:

- Cases and controls were selected from the 5 main European nuclear facilities (located in Belgium, France, and United Kingdom) where workers had potential for internal incorporation of U and/or Pu. Eligibility of cases and controls were determined by criteria defined in the Common Study Protocol. Demographic and risk factor 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.
- Approaches for taking into account errors and uncertainty in doses were developed.
- An existing software programme (IMBA Professional, Alpha Risk version) were substantially modified to allow dose reconstruction with the common dose reconstruction approach within WP3
- A new software programme for the dosimetric uncertainty analyses, “Uncertainty Analyser” was developed.
- Standard conditional logistic regression models were employed to analyze data, using linear relative risk models in which the relative risk was assumed to be of the form 1+ßZ (Z = lagged cumulative dose, ß = excess relative risk (ERR) per mGy), and on log-linear models, in which the relative risk is of the form exp(ßZ).
- 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 leukemia 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 (results are confidential until publication) and a number of scientific manuscripts are in preparation and will be submitted shortly for publication.

The Work package 4, The Feasibility of a joint mortality study of the cohorts of UK-BNFL and French (CEA-AREVA) plutonium and uranium workers, resulted in the following reports:

- 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 in the WP3 case-control study.
- Elaboration of the common protocol to produce plutonium and uranium organ specific doses in accordance with a methodology agreed by a European Union Internal Dosimetry Committee of experts.

Work package 5, Organ doses, produced numerous outcomes, namely:

- Analysis of exposure uncertainty in radon studies
- Assessment of inter-subject variability in lung dosimetry
- Assessment of lung dosimetry models for radon progeny inhalation
- Assessment of lung dosimetry model for uranium dust inhalation
- Assessment of organ dosimetry for radon progeny and long-lived radionuclides
- Assessment of exposure conversion factors for radon exposures in mines and homes
- Analysis of dose uncertainty by comparison of different dosimetry models
- Analysis of dose calculations and risk assessment for dose-response modeling

Within Work package 6, Integration of results, the main findings were as follows:

Related to the comparison of radon-related lung cancer risks:

- The European case-control miner data support the BEIR VI finding that the excess relative risk (ERR) due to radon decreases significantly with increasing time since exposure. No such trend is apparent in the European residential data. In part, this may reflect the higher coverage of more recent exposures in the European residential data, whereas the miner data have higher coverage of exposures in the distant past.
- 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.
- In order to equate findings from epidemiological studies in mines (expressed as cumulative exposure in WLM) with those from studies in homes (based on time-weighted average radon concentrations, Bq m^{-3}), then assuming 7000 hours spent indoors per year and an equilibrium factor of 0.4, it was assessed that exposure at 100 Bq m^{-3} over 30 yrs is equal to 13.2 WLM.
- The proposed risk model from WP6 is a modified version of the BEIR VI Exposure-Age-Concentration model, fitted to the European miner case-control data below 300 WLM. 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. No adjustment is made for the

effect of exposure rate; the focus here is on application to low exposure rates. Both multiplicative and sub-multiplicative models for the joint effect of radon and smoking on the ERR are considered.

Related to the 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-EAC model gives the highest values. The lifetime risk estimates from the WP6 and WP1 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. As expected, the lifetime risks increased with increasing radon exposure and were slightly higher when summed up to age 80 years than to age 75 years.
- *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 is 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. However, under a sub-multiplicative model, the lifetime risk of radon-induced lung cancer is still substantially higher for continuing smokers than for never-smokers (by around a factor of 5-7).
- *Effect of radon mitigation*: Consideration of alternative exposure scenarios indicates that, even for persons 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.

Dissemination of 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 and are of high value in support to occupational epidemiology and protection of workers.

The findings from the performed research are likely to be of value to (i) epidemiologists and health economists interested in the effects of indoor radon on lung cancer risk; (ii) radiation protection officials wishing to examine the implications

for advice on protection from radon in dwellings, including remediation; (iii) public health officials responsible for programmes to reduce lung cancer death rates.

The findings from studies of lung cancer following residential and occupational radon exposures are generally compatible (within a factor of around 2). This is an important result for risk estimation. Furthermore, it has been found that, in absolute terms, the risk of lung cancer from radon exposure is much higher among smokers than non-smokers. These results should provide a valuable input to radon remediation and lung cancer prevention programmes in Europe. This information may be used in risk management, including exposure assessment and consideration of exposure limits.

The results obtained within the Alpha Risk project were presented at the Alpha-risk Open scientific meeting in Paris on 23 October 2009. These findings will continue to be disseminated by publications in the scientific literature and presentations at scientific congresses. As well as notifying epidemiologists and public health professionals of these findings, attempts will be made to reach a wider audience.

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. The similar extension of organ dose calculation to nuclear workers populations was shown to be feasible within WP3 and WP4.

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.

The lifetime risks calculated in WP6 are based on a generic life table and for individuals rather than populations. Extending these calculations to cover populations of European countries would require additional information or simplifying assumptions about changes over time in the proportions of continuing, ex- and never-smokers, as well as the associated impact on lung cancer and all-cause mortality rates. Such calculations would be valuable in assessing how risks vary according to the different exposure distributions in various European countries.

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 and 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 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 allows 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.

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