Research project "UMINERS + ANIMAL DATA"

Quantification of lung cancer risk after low radon exposure and low exposure rate: synthesis from epidemiological and experimental data

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Project funded by the European Community
under the Fifth Framework Programme
Contract N° : FIGH-CT1999-00013

February 2000 - August 2003

FINAL TECHNICAL REPORT

CONTRACT N° : FIGH-CT1999-00013

PROJECT N° :

ACRONYM : UMINERS + ANIMAL DATA

TITLE : QUANTIFICATION OF LUNG CANCER RISK AFTER LOW RADON EXPOSURE AND LOW EXPOSURE RATE : SYNTHESIS FROM EPIDEMIOLOGICAL AND EXPERIMENTAL DATA

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REPORTING PERIOD : FROM February 2000 TO August 2003

PROJECT START DATE : February 2000 DURATION : 42 months

Date of issue of this report : September 2003

Project funded by the European Community under the Fifth Programme (1998-2002)

LIST OF ACRONYMS

AEAT	AEA Technology Plc (United Kingdom)
AME	Age at Median Exposure
BEIR	Biological Effects of Ionizing Radiation
BfS	Bundesamt für Strahlenschutz (Germany)
CEA	Commissariat à l'Energie Atomique (France)
CEAR	Cumulated Excess Absolute Risk
CERR	Cumulated Excess Relative Risk
CI	Confidence Interval
COGEMA	COmpagnie GEnérale des MAtières radioactives
CR	Cumulated risk
EC	European Community
ERR	Excess Relative Risk
FP	Framework Programme
GSF	Forschungszentrum für Umwelt und Gesundheit (Germany)
ICD	International Classification of Diseases
IH	Integrated hazard
ILO	International Labour Organisation
IP	Initiation – Promotion (TSCE model)
IRSN	Institut de Radioprotection et de Sûreté Nucléaire (France)
IT	Initiation – Transformation (TSCE model)
JEM	Job Exposure Matrix
LEAR	Lifetime Excess Absolute Risk
LERR	Lifetime Excess Relative Risk
MVK	Moolgavkar, Venzon and Knudson (TSCE model)
NRPB	National Radiological Protection Board (United Kingdom)
NRPI	National Radiological Protection Institute (Czech Republic)
OR	Odds Ratio
PAEC	Potential Alpha Energy Concentration
PNNL	Pacific Northwest National Laboratory (USA)
PY	Person-Years
RIVM	National Institute of Public Health and the Environment (the Netherlands)
RR	Relative Risk
SMR	Standardised Mortality Ratio
TMC	Two-Mutation Carcinogenesis
TME	Time Since Median Exposure
TSCE	Two-Stage Clonal Expansion
TSE	Time Since Exposure
WHO	World Health Organization
WLM	Working Level Month
WP	Work-Package

PLAN

EXECUTIVE SUMMARY

INTRODUCTION

Radon is a radioactive gas produced during the decay of uranium 238 that is present in soil. It was classified as a human lung carcinogen in 1988, based on evidence both from animal studies and from human studies of miners with high levels of radon exposure. Radon is present everywhere; therefore the quantification of the risk associated with exposure to it is a key public health issue.

OBJECTIVES

The project aimed to analyse the risk associated with radon inhalation at low doses and at low rates of exposure. It involved researchers from three different fields: epidemiology, animal experiments and mechanistic modelling and provided a unique opportunity to study the influence of dose-rate, mainly in the range of low daily exposures over long periods, by analysing in parallel results from both animal and epidemiological studies. The project comprised 6 work-packages (WP). Firstly, the partners involved in epidemiology and animal experiments worked on the validation and the analysis of the data. Secondly, the data from WP1 and WP4 were transferred to the partners involved in WP5 for the application of mechanistic models. In the final step a synthesis of the results was prepared.

DESCRIPTION OF THE RESEARCH PERFORMED

WP1 - epidemiology of uranium miners in Europe: The main objective was the quantification of the dose-response relationship between radon exposure and lung cancer risk among European miners exposed to low doses or at low dose rates of radon decay products. An associated objective was to investigate how time dependent factors like attained age, age at exposure and time since exposure may modify this relationship. Data were obtained from French, Czech and German cohorts of underground uranium miners. These data were reviewed and various selection criteria applied to ensure good quality of exposure assessment and low levels of cumulative exposure.

The German cohort includes 17 162 miners employed since 1971. Data collection has been completed during this project, and the analysis of risk will be performed in the near future.

The French and Czech cohorts jointly comprise more than 10 000 miners, with a mean cumulative exposure of 48 working level months (WLM). The mean duration of follow-up was 24 years, with 574 lung cancer deaths. An excess of lung cancer deaths was observed, increasing with the level of cumulative exposure and the excess relative risk per WLM decreased with age at exposure and time since exposure. A significant effect of the method of exposure assessment (retrospectively estimated versus measured) was also observed. A model incorporating these modifying factors as continuous variables was proposed. After adjustment, no effect of exposure rate was observed.

WP2 – Nested case-control studies: A major risk factor for lung cancer is tobacco consumption, but this information is generally missing or sparse among miner cohorts. The main aim of WP2 was to define three nested case-control studies from the French, Czech and German miner cohorts, and to collect retrospectively data on radon exposure and tobacco consumption. Together, the three studies included more than 1100 cases and 2600 controls. The project demonstrated that it was difficult to reconstruct past tobacco consumption among miners. A preliminary analysis of the Czech data suggests there is a sub-multiplicative interaction between the effects of radon and smoking on lung cancer risk.

WP3 - combined analysis of occupational and indoor exposure: The objective of this work-package was to collect detailed information on possibly important confounders like smoking habits, indoor radon exposure and occupational exposure to silica, for former uranium miners who participated in a case-control study in Germany. The study (486 lung cancer cases and 898 controls) will allow an

analysis of the joint effect of radon exposure in mines and smoking. In conjunction with contract FIGH-CT-1999-000008 “Radon Epidemiology”, interviews were conducted in a subset of 250 miners and glass-based radon measurements were performed in their homes. Chest x-rays of 358 cases and of 469 controls were examined in order to classify the status of silicosis.

WP4 – Animal data: Under the Fourth European Community Framework Programme, a new series of experiments was carried out to investigate specifically the influence of radon exposure rate on lung cancer induction in rats. These studies were conducted at relatively low cumulative exposures, which are comparable to current underground mining exposures. The animal experiments were conducted concomitantly in France and in the UK, and comprised more than 4000 exposed rats and 1500 non-exposed control rats. The analysis of histopathology to define fatal lung tumours during lifetime follow up was standardised.

At low cumulative exposures, the risk of lung cancer was observed to increase with increasing exposure rate. At high cumulative exposures (>100 WLM), the reverse was observed (decreasing risk with increasing exposure rate), in agreement with earlier findings.

WP5 - mechanistic modelling of lung tumour development after radon exposure: Mechanistic modelling was used to describe the risk of lung cancer associated with radon exposure, and to determine the particular stages of carcinogenesis on which the effect of radon was strongest. Analyses were applied to both rat and miner data provided by WP4 and WP1. Historical data were also considered.

For the animal data, the feasibility of combining the datasets and thus increasing the overall statistical power of the data was tested. It was found that both the initiation-transformation and the initiation-promotion models fitted the various datasets equally well when all tumours were assumed to be incidental.

For the human data, the feasibility of pooling the data was also examined. One finding was that the Czech and French miner datasets could be pooled and modelled together if separate baseline risks were incorporated. The application of mechanistic models to this combined dataset led to a strong initiation term and to a transformation term that was one order of magnitude lower. A different form of the mechanistic model found a strong promotion effect of radon. The effects of dose rate and dose protraction were also examined. The suitability of using nested case-control datasets selected from cohorts was examined and rejected.

WP6 – Synthesis of results from human and animal data: The aim was to present a synthesis of the results from both animal and human data and from both epidemiological and mechanistic modelling.

Good agreement was found between the results from both the animal and human data. Both types of data demonstrated the existence of an increased risk of lung cancer associated with cumulative radon exposure. No inverse exposure rate effect was observed at low levels of exposure.

From the animal data, the results of mechanistic modelling show a much larger impact of radon on initiation (first mutational step) rather than on transformation (second mutational step) in the process of carcinogenesis. The results of modelling the human data agree with this but a strong effect of radon on promotion (clonal expansion) was also possible.

Results from classical epidemiological analyses and mechanistic modelling converged to show a significant exposure-risk relationship, with a modifying effect of time since exposure or age at exposure. The Figure below illustrates the relative risks predicted by the different models on a specific miner scenario, and compares these with the risks estimated using the preferred models from the BEIR VI report.

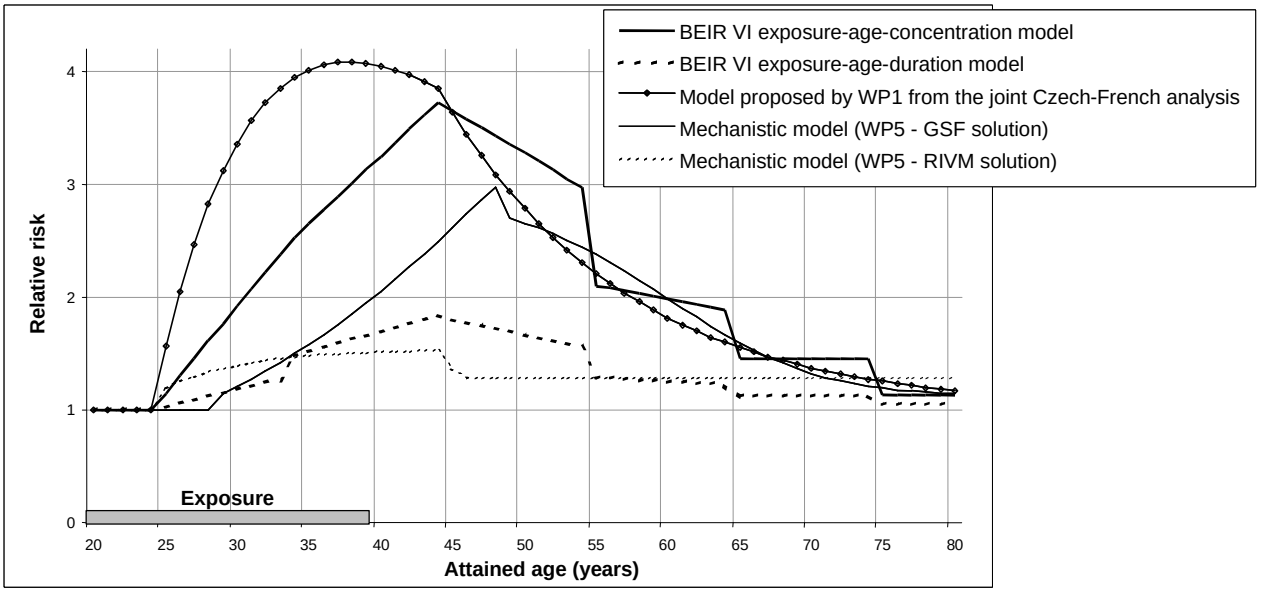

Figure: Relative risk according to age for a constant exposure to 2 WLM per year over 20 years, from age 20 to 39, estimated by different models

One of the main aims of the project was to construct a large dataset with low levels of exposure, protracted over a long duration. Using these data, the degree of extrapolation required to predict risks in the general population is less than when using previous analyses of miners data. The models derived from the joint analysis of Czech and French miners in WP1 and WP5 have been used to estimate the risk of lung cancer death attributable to indoor radon exposure. The estimated lifetime excess relative risks are similar between the different models, and are also consistent with those obtained with the BEIR VI preferred models.

MAIN ACHIEVEMENTS

Production of new datasets (human and animal) to analyse the effect of radon at low exposure rates: The project enabled the construction of three cohorts of miners with low levels and long duration of exposure to radon. Together, these include more than 27 000 miners for whom a follow-up of individual exposures was obtained. Also, four case-control studies have been developed among uranium miners, including a total of more than 1600 cases and 3600 controls. Reconstruction of cumulative radon exposure and past tobacco consumption for these studies is nearing completion. The project enabled the finalisation of data from experiments including a total of more than 4000 rats (plus 1500 control rats) exposed to various exposure rates under controlled conditions. The animal databases will be transmitted to the European Radiobiology Archives and made available to other researchers.

Quantification of the relationship between radon exposure and the risk of lung cancer death, taking account of potential risk modifiers: These data provide the necessary statistical power to quantify the relationship between radon exposure and the risk of lung cancer. The joint analysis of the Czech and French miner cohorts confirms the existence of an increased risk of lung cancer death associated with cumulative radon exposure. The excess relative risk per WLM was found to decrease with increasing time since exposure and age at exposure. Mechanistic modelling of the same data showed good agreement in the estimated risks. These results are consistent with the results of previous analyses performed at higher levels of exposures. The mechanistic models proposed in this project could be used to assess the lung cancer risk associated to indoor exposure among the general population.

Production of new knowledge on the effects of radon exposure at low exposure rate and low cumulative exposure, through the parallel analysis of animal and human data: Previous results from both human and animal studies suggested the existence of an inverse exposure rate effect in the relationship between radon and lung cancer risk. Results obtained in our project from animal and human data are in agreement: no effect of exposure rate was observed at low levels of exposure, but an inverse dose rate effect cannot be excluded for high exposure rates and high levels of cumulative

exposure. Mechanistic modelling of both animal and human data enabled investigation of the role of radiation in the carcinogenesis process.

EXPLOITATION AND DISSEMINATION OF THE RESULTS

The project deliverables have been widely disseminated in the scientific literature. By the end of the contract, the project had led to more than 50 scientific publications or communications. Twenty-five additional publications or communications to scientific congresses are in preparation or scheduled over the next three years.

The users of the results are epidemiologists, health economists and researchers interested in the assessment of the effects of radon on lung cancer risk. The results are also of interest to those concerned with radiation protection for those exposed to enhanced radon levels in the workplace or in the home. Public health officers responsible of lung cancer prevention programmes could also be interested.

PERSPECTIVES

Continuation of the follow-up of the cohorts into the future will improve the estimation of lifetime mortality risks, and will allow a better determination of the time dependency of the dose-response relationship. The inclusion of additional follow-up will increase the statistical power of the joint analysis of the French, Czech and German studies and the ability of this analysis to detect small variations in risk. The work performed in the recent years on the cohorts and the case-control studies has allowed the collection of data on other exposures (external gamma radiation, long-lived radionuclides in ore dust, diesel exhaust, arsenic, indoor radon concentration) and other risk factors (tobacco consumption, silicosis). These data will allow a multifactorial analysis to be carried out.

Some work should be performed on the calculation of organ dose, considering combined sources of exposure. This work is also needed to improve the comparison of results from animal and human data.

Collaboration between epidemiologists and mechanistic modellers should be continued in the future. It was not possible to analyse data on smoking in the French, Czech or German cohorts in the framework of the present project. Further collaboration is needed to allow mechanistic modelling of the combined effect of radon and tobacco on lung cancer risk among miners. This collaboration is also needed to assess the different methods of risk extrapolation from miners to the general population. A comparison of the results with those from the European project on indoor radon studies (FIGH-CT-1999-000008) should also be performed in order to synthesise all the available knowledge on the effects of radon exposure.

CONCLUSION

The project involved three different fields of research: epidemiology, animal experiments, and mechanistic modelling. The collaboration allowed the exchange of data between the different partners, and permitted fruitful discussions between researchers with different background and an internal critical assessment of the data quality and of the results. This tight collaboration was a necessary basis to succeed in synthesising the results obtained from both human and animal data. Such a multidisciplinary approach should be continued in the future, and may be extended to other fields of research.

The project has led to a better knowledge of the effects of radon inhalation, and provides more information about factors that modify the associated lung cancer risk. The synthesis of the results of both human and animal data represents the state-of-the-art knowledge on the effect of radon exposure in miners at relatively low doses and low dose rates. This in turn should assist in the management of radon exposures and in formulating advice on lung cancer prevention. As a consequence, a net benefit to health is expected.

Miners cohorts provide information on a large population (27 000 individuals), with good quality of follow-up (<3% lost to follow-up) over a long duration (> 24 years), and with precise estimates of individual exposures. These data constitute a very good basis to quantify the risks associated with chronic exposures to radiation at a relatively low dose rate. The size of the datasets, the long term follow-up and the quality of exposure data ensure the capability to detect low risks, and to determine the impact of effect modifiers. Long term follow-up will allow the analysis of potential risks for non cancer causes of death. Furthermore, the work performed in the recent years has allowed the collection of data on other risk factors. These data will enable a multifactorial analysis of risk, and the consideration of the effects of both internal and external radiation exposure.

INTRODUCTION

Radon is a radioactive gas produced during the decay of uranium 238 that is present in soil. It can concentrate in stuffy atmospheres like in mines. Elevated concentrations can be measured in some buildings, depending on the nature of the subsoil, type of construction, building material, inhabitants habits, etc. Radon can be inhaled, and its daughters can induce irradiation of lung and bronchial cells. Radon has been classified as a lung carcinogen for humans since 1988 [IARC 1988]. This statement was based on evidence coming from animal data and from uranium miners studies with high levels of exposure to radon.

Since the 1970s, a large number of miners cohorts studies have been published. A comprehensive analysis of 11 cohorts has been published [Lubin 1994, BEIR VI 1999]. The Czech and French cohorts of miners were already involved in this joint analysis [Tirmarche 1993, Tomasek 1994]. The results consistently demonstrate an excess risk of lung cancer death associated with radon exposure. However, a large proportion of these results are based on high radon exposures, received during a short period of exposure. Furthermore, the existence of an inverse exposure rate effect on the relationship between radon exposure and lung cancer risk was suggested. This effect was reduced when analyses were performed on data with restricted exposure ranges [Lubin 1995]. No direct verification of an exposure rate effect has been possible on long-term follow-up data. An inverse dose rate effect was also observed in previous analyses of animal experiments performed at high levels of exposure and exposure rates [Chameaud 1984, Cross 1999].

The project "UMINERS+ANIMAL DATA" aimed to analyse risks associated with radon inhalation at low level and low rate of exposure. It involved researchers from three different fields: epidemiology, animal experiments and mechanistic modelling. It gave the opportunity to study the influence of dose-rate effect, mainly in the range of low daily exposures over long periods, by analysing in a parallel way, results from animal and from epidemiologic studies.

The project constituted an extension of researches initiated in the frame of the Fourth EC FP [Tirmarche 1999, Tirmarche 2001, Monchaux 2001]. It consisted of 6 work-packages. Figure 1 summarises the organisation of the project into work-packages.

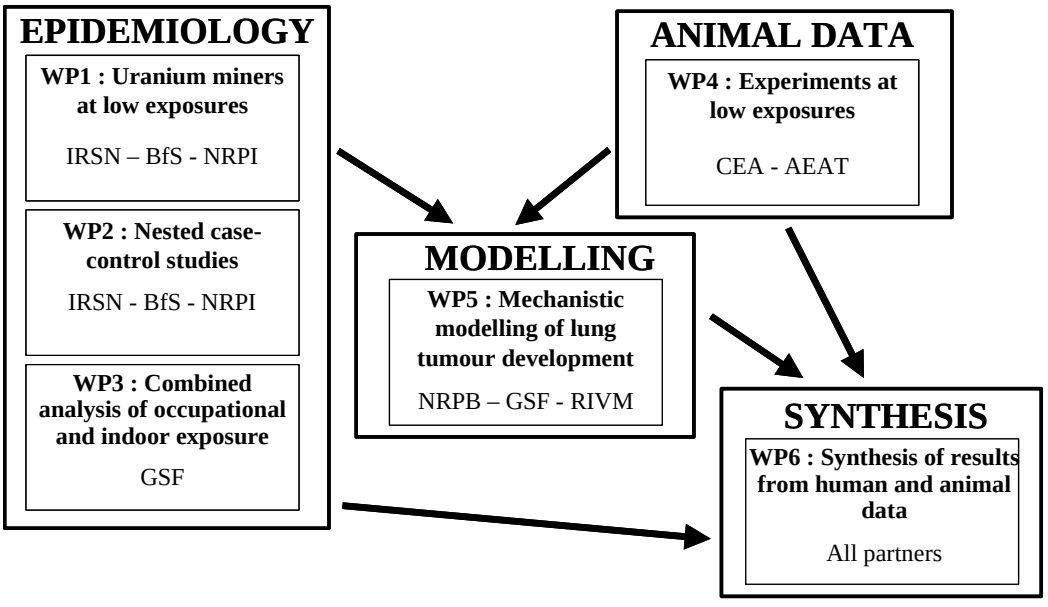

Fig. 1 : Organisation of the project into work-packages

Work-package 1 aimed at studying epidemiologic data from miners' cohort studies. The report presents the results of the analysis of the French and Czech cohorts (IRSN and NRPI), and the completion of the German Wismut cohort (BfS).

Work-packages 2 and 3 aimed at considering other risk factors of lung cancer, and especially at assessing the interaction between radon and tobacco consumption among miners, using case-control studies. The report details the data collected among the German (BfS and GSF), French (IRSN) and Czech studies (NRPI) and presents a preliminary analysis of the risk associated with radon and smoking. Additional objectives included in WP3 (GSF) concerned the measurement of indoor radon exposure and the evaluation of silicosis among miners.

Work-package 4 aimed to analyse the risks associated with radon exposure from animal experiments. The report presents the results of experiments conducted on rats in France (CEA) and England (AEAT), and includes the analysis of the effects of dose rate on the risk of lung tumour.

Work-package 5 aimed to analyse both animal and human data, based on mechanistic modelling. The report presents the results obtained by GSF, NRPB and RIVM on data from both animal experiments and miners cohorts. Data from previous studies are also considered in several analyses.

Work-package 6 aimed to synthesise results from human and animal data, on the basis of the results from the first 5 work-packages.

This final technical report presents the achievements for the whole period of the contract, from February 2000 to August 2003. The material, methods, results and production are described by work package.

WORK PACKAGE 1: EPIDEMIOLOGY OF URANIUM MINERS IN EUROPE

Principal contractor: BfS, B. Grosche
Participants: IRSN (A. Rogel, D. Laurier, M. Tirmarche), BfS (M. Kreuzer, M Schnelzer, A Tschense), NRPI (L. Tomasek)

OBJECTIVES

The overall goal of Work-Package 1 is the evaluation of the lung cancer dose-response relationship and of dose rate effects among European uranium miners exposed to low doses or low dose rates of radon decay products. Included miners are respective miners from the French and Czech cohorts and those from the youngest cohort of the German miners, i.e. those who started work in 1971 or later (sub-cohort C). An associated objective is to investigate how time dependent factors like attained age, age at exposure and time since exposure may modify the risk of lung cancer associated with radon exposure [Lubin 1994, BEIR VI 1999]. For this purpose, the joint analysis will increase the statistical power and allow a more detailed description of the variation of dose-response relationship according to time.

In France, analysis of the French cohort of uranium miners started in 1980, with a first cohort analysed in 1993 [Tirmarche 1993], based on 1785 miners. Enlargement and extension of the length of follow-up and the results of the mortality study have been presented within EC's 4th Framework Programme. The analysis presented here is based on 5098 miners. The Czech cohort study was established in 1970 and firstly reported in 1971 [Ševc 1971]. Since then more than 20 papers were published. In 1980, the original cohort was extended by another cohort of uranium miners exposed to low levels of radon. The cohort was periodically analysed in the frame of nine research projects of the Czech Ministry of Health (1972 - 2000). In Germany, uranium mining was conducted from 1946 to 1989. As much as several hundreds of thousand miners were employed. Based on some 130 000 individually known miners, a cohort of 64 000 employees was defined. A follow-up was conducted until the end of 1998. In this report, first results are presented for approximately one quarter of this cohort, comprising employees who were employed 1971 or later and subsequently exposed only to low levels of radiation.

1. DEFINITION OF THE STUDY POPULATION

Table WP1.1 gives information on the three study populations. The French cohort includes 5098 miners employed at least one year as a miner in the French uranium mines since 1952 and followed up to 1994, Dec. 31. The follow-up starts one year after employment. The Czech cohort includes 5002 miners who started work since 1952 and worked for at least four years underground. For them, follow-up began earliest 1956 and ended 1995, Dec. 31. The 17 162 employees included in the German study had to work for at least 180 days for the mining company with a date of first employment between 1971 and 1989. The follow-up period covers the years 1971 to 1998.

Figure WP1.1 presents the location of mines in Europe. In France, there are several locations: in Vendée, in Limousin, in Herault, and in Forez. There are also mines in Africa (not shown on the map). In the Czech Republic, places of mines were scattered over the West and North West of its territory. In Germany, mines were located in the southern parts of the former Eastern Germany, i.e. in Saxony and Thuringia.

Table WP1.1: Initial cohort size, inclusion criteria, and cohort selection by country

	France	Czech Republic	Germany
Sex	Male	Male	Male
Period of employment in mines	1946-1992	1952-1974	1971-1989
Employment status, facility	Miners at COGEMA-CEA group	Underground miners Czechoslovakian Uranium Industry	SDAG Wismut
Minimum length of employment	1 year	3.5 years	180 days
Minimum length of exposure	No	4 years	no
Maximum level of exposure	No	no	no
Size of initial cohort	> 7000	9960	59 161
Size of cohort after criteria	5098	5002	17 162

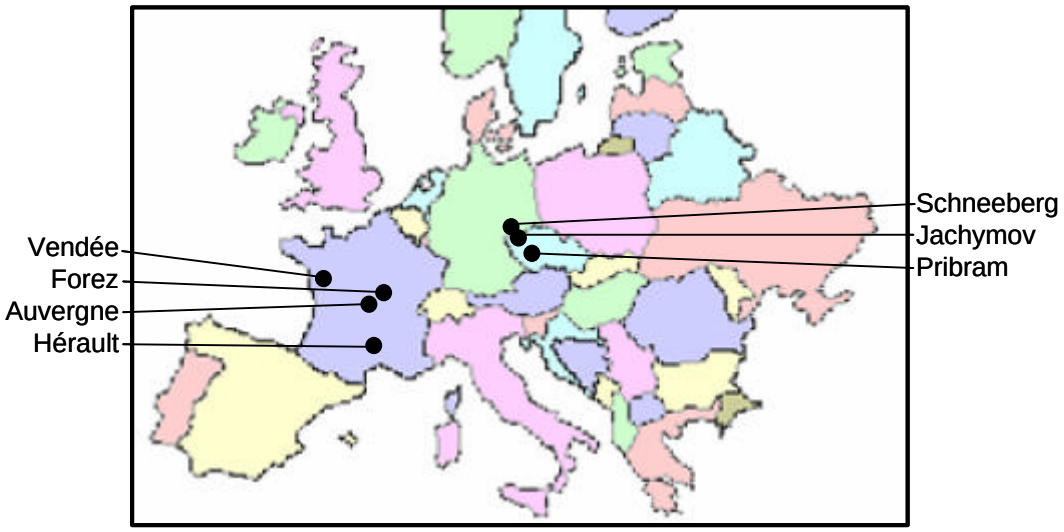

Fig. WP1.1: Approximative location of uranium mines in Europe

2. VITAL STATUS AND CAUSES OF DEATH

Table WP1.2 presents the methods of follow-up and cause of death ascertainment for the three cohorts. In France, vital status has been ascertained by information from the administrative and medical files of COGEMA. For each miner suspected to have died or with an unknown status, validation of the vital status has been asked to the town hall of the place of birth, or to the ministry of foreign affairs for those miners born outside France. Information on causes of death has been collected from two complementary sources, depending on the period. For the first period (1946-1985), causes of death were collected through an active research by the occupational medical service of COGEMA. Since 1986, it is possible to use an anonymous linkage procedure with the French national mortality database to gather information from death certificates. All causes of death were coded according to the International Classification of Diseases (ICD). Causes of death have been obtained for 1092 deaths (94%). In the Czech Republic, information on vital status was derived from various sources, namely the Ministry of the Interior, the Social Security Office, and local administrations. Information on causes of death was collected from local death registries. In Germany, the follow-up on vital status was conducted via several administrations, e.g. local administrations, local health authorities, district archives, and – for some 3000 deceased miners – the German Cancer Research Centre. This Centre holds the Wismut pathology archive. Basically, information on causes of death were collected via local health authorities and district archives, but again the pathology archive was used as additional source of information.

Table WP1.2: Methods of follow-up and cause of death ascertainment

	France	Czech Republic	Germany
Sources for follow-up	Administrative files of COGEMA, Registries, town halls at place of birth	Administrative files of Czechoslovak registry at the Ministry of the Interior, Social Security Office, Local administrative files	Administrative files from various sources, e.g. Local Registration Office, Local Health Administration, District Archives, German Cancer Research Centre
Death ascertainment	National file of causes of death; when incomplete, medical files from COGEMA	Local death registries	cause of death certificate; or autopsy finding

As can be seen from Table WP1.3, the percentage of miners lost to follow-up was 2.3%, 2.7%, and 2.1% for the French, Czech, and German cohort, respectively. Thus, for all three cohorts there was a successful follow-up. The number of lung cancer deaths in the three cohorts was 125, 449, and 18, respectively.

Table WP1.3: Population size and follow-up

	France	Czech Republic	Germany
Population size	5098	5002	17 162
Follow-up period	1946 – 1994	1956 – 1995	1971 – 1998
Person-years	133 521	115 261	304 091
Vital status			
lost to follow-up	117 (2.3%)	137 (2.7%)	346 (2.1%)
dead	1162 (22.8%)	1913 (38.2%)	639 (3.7%)
death from lung cancer	125 (2.5%)	449 (9.0%)	18 (0.1%)
alive at end of study (%)	3819 (74.9%)	2503 (59.0%)	16 177 (94.3%)
Mean (min-max) in year			
length of follow-up	26.2 (0.1 – 48.7)	23.2 (0 – 40.0)	17.7 (0.0–27.5)
age at entry in study	28.8 (16 – 68)	32.9 (19 – 67)	20.7 (13 – 73)
age at end of study	55.0 (19 – 85)	56.1 (21 – 84)	38.9 (16 – 94)
age at death	59.2 (21 – 85)	59.5 (21 – 84)	37.0 (17 – 90)
age at death from lung cancer	61.8 (43 – 81)	58.3 (28 – 83)	47.4 (34 – 63)

3. EMPLOYMENT AND EXPOSURE IN URANIUM MINES

Table WP1.4 presents the description of employment for all the cohorts. Since the French cohort goes most far into the past, the duration of employment was highest here, whereas it is shortest for the relatively young German cohort.

Table WP1.4: Description of employment

Mean (min-max) in years	France	Czech Republic	Germany
Duration of employment	15.6 (1.1 – 42.3)	9.1 (3.6 – 36.6)	7.6 (0.5 – 19.0)
First year of employment	1963 (1945 – 1989)	1962 (1952 – 1974)	1979 (1971 – 1989)
Age at 1st employment	27.4 (14 – 67)	28.6 (13 – 63)	20.7 (13 – 73)
Age at end of employment	43.0 (16 – 74)	38.8 (20 – 69)	28.2 (16 – 81)

As can be seen from Table WP1.5, exposure estimates for the cohorts are based on slightly different approaches. For the French cohort, reconstruction of radon exposure has been completed for the miners up to 1995. The work has been performed in close collaboration with COGEMA, which has ensured continuous dosimetric monitoring of all uranium miners since the beginning. The method for

exposure assessment changes with calendar period. For the first period 1946-1955, annual exposures have been retrospectively determined by a working group of experts using an ambience measurement multiplied by characteristics of mines, duration and location of work of each miner. Since 1956, recording of the annual radon exposure of all workers has been systematic. Each exposure variable was registered in the miner's file as individual annual exposures [Laurier 1999, Tirmarche 2000]. For the Czech cohort, radon measurements exist since 1949, and individual exposure data are available since 1968 [Placek 1997]. For French and Czech cohorts, method of exposure assessment is labelled 'Measured' when based on individual measurements, and 'Estimated' otherwise. For the German cohort, exposure estimates are based on a job-exposure matrix, which has been developed by the Miners Occupational Insurance Board. Amendments were necessary for the years until 1961 and are available since July 2003, but that does not affect the German miners included in WP1, since their first day of employment was not before 1971. In any of the three cohorts, some additional information is available, e.g. on other exposures in the uranium mines, or on exposure to radon before employment in the mines.

Table WP1.5: Methods of exposure measurement

	France	Czech Republic	Germany
Sources of exposure data	Exposure file from COGEMA	Employment files including duration, job, and location of mine	Job-Exposure-Matrix; quasi-individual measurements for hewer, estimates for other jobs
Method of Exposure assessment	Before 1956, retrospective environmental measurements assessed by a group of experts 1956-82 individual records filled in during work and kept in the mines	Radon measurements since 1949, individual exposure data since 1968	radon measurements at the work place, estimates for different jobs
Data on other exposures in U mines	After 1956, individual records of gamma rays and dust	Partly (30%) gamma, dust, long lived activity since 1970	gamma, long-lived radionuclides, dust
Other underground exposure to radon	Exposure before employment: known for 112 study subjects, assumption for 1911 study subjects	hard rock mining according to measurements in the middle 1960s	sometimes known

Table WP1.6 presents radon exposure characteristics. Among the 4134 French miners with positive radon exposure, mean cumulative exposure is 36.5 WLM[1], protracted on a mean duration of 11.5 years. Thirty-two lung cancer deaths have cumulated a total exposure below 50 WLM, 70 have a mean exposure rate below 0.5 WL. Figures WP1.2 and WP1.3 present the mean annual exposure to radon and the mean exposure rate, respectively, over time. For the French cohort, there is a sharp decrease in radon exposures after 1956, following the introduction of radiation protection measures such as forced ventilation in mines. Mean exposures decreased from more than 20 WLM/y during the period 1946-1955 to less than 4 WLM/y after 1956. Mean annual exposures in the Czech study progressively decreased from about 15 WLM/y to 7 WLM/y in the period 1952-67 and were about 1 WLM/y afterwards. For the German cohort, the exposure situation was pretty stable during the years under study. The average exposure was about 1.4 WLM/y.

[1] WLM (Working Level Month): unit of exposure multiplying a concentration of radon decay products by the duration of exposure. A monthly exposure of 1 WLM is defined as 170 working hours in an atmosphere of 1 WL. 1 WL is equivalent to any combination of radon decay products in 1 liter of air, that results in the emission of 130 000 MeV of energy of α particles.

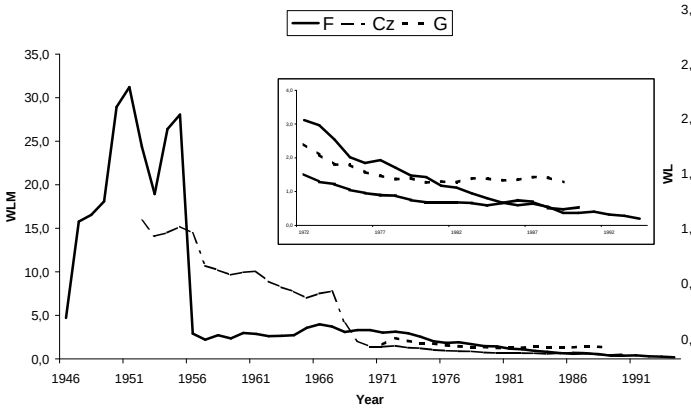

Fig. WP1.2: Mean annual exposure by cohort

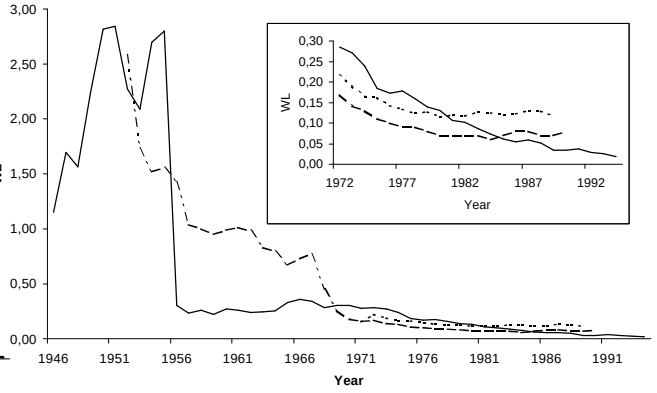

Fig. WP1.3: Mean annual exposure rate by cohort

The collective exposure was highest in the Czech cohort and lowest in the German one. Due to the large size of the cohort, it was intermediate in the German cohort, even though the number of exposed years was smaller than in the others. The proportion of measured exposures in terms of collective exposure was 53% in the French study, in other two studies was close or equal 100%.

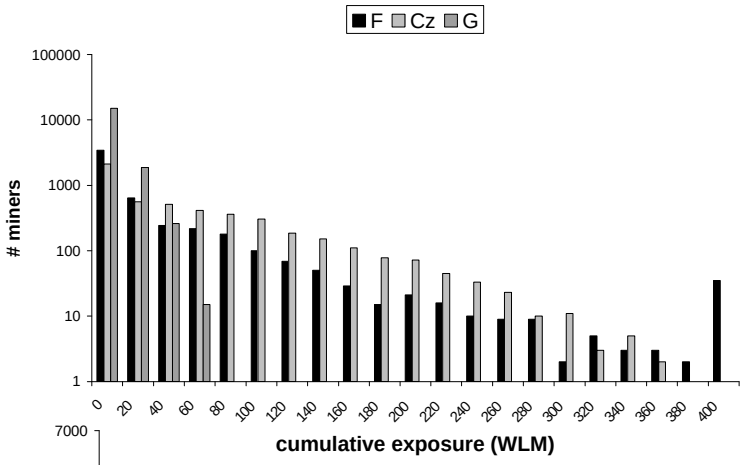

Fig. WP1.4: Number of miners by WLM and cohort (y-axis in logarithmic scale)

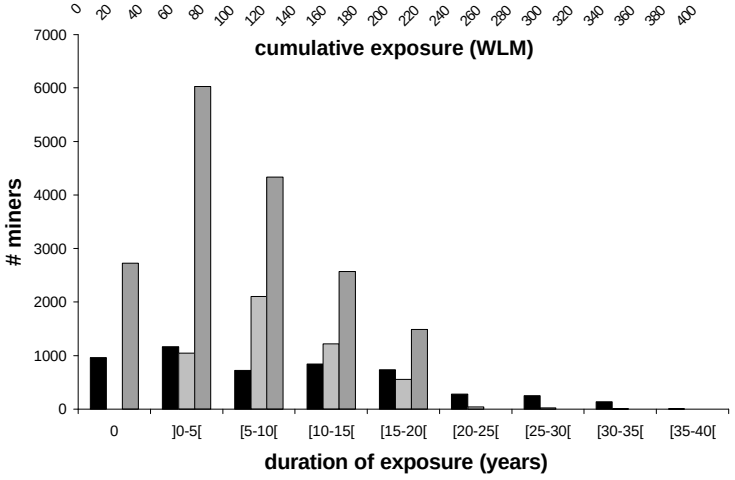

Fig. WP1.5: Number of miners by number of years of exposure and by cohort

Figure WP1.4 shows the distribution of miners by total cumulative exposure, while Figure WP1.5 shows the distribution of miners by duration of exposure.

Table WP1.6: Radon exposure

	France	Czech Republic	Germany
Number of non-exposed miners	964	0	2727
Mean (min-max) among exposed			
cumulative exposure (WLM)	36.5 (0.1 – 960.1)	57.3 (0.3 – 386.7)	9.6 (0.1-65.4)
positive annual exposure	3.6 (0.01 – 110)	0.67 (0.01 – 4.8)	1.4 (0.1 – 6.9)
duration of exposure (y)	11.5 (1 – 37)	9.1 (3.6-36.6)	6.7 (1 – 19)
age at 1st exposure (y)	29.1 (15 – 65)	28.6 (13 – 63)	21.5 (15 – 61)
age at last exposure (y)	40.8 (16 – 65)	38.8 (20 – 69)	27.3 (16 – 63)
Number (%) among exposed			
lung cancer deaths	125	449	16
lung cancer death and			
50-100 WLM cumulative exp.	50 (40.0 %)	139 (31.0%)	2 (12.5 %)
<50 WLM cumulative exp.	32 (25.6%)	72 (16.0%)	14 (87.5 %)
Collective exposure (manWLM)	151 085	272 356	138 203
estimated	70 844	1802	0
measured	80 241 (53%)	270 554 (99%)	138 203 (100%)

5. DESCRIPTION OF MORTALITY

Due to the fact that data from the first follow-up for the German cohort were only available by the end of 2002, not all information was available at the time of writing this report. Thus, some of the information can be given only for the French and the Czech cohorts.

5.1 General mortality

Table WP1.7 presents observed deaths, expected number of deaths calculated by applying male national rates, and Standardised Mortality Ratios (SMR) with 95% confidence intervals (95%CI) for all causes of death and for selected causes. No healthy worker effect is observed in the French and in the Czech cohort. While the SMR for the French cohort is close to unity, overall mortality is significantly elevated by 41% in the Czech cohort. Compared to expected numbers based on mortality data from the general public, significant excesses are observed for all cancers (SMR=1.14; 95%CI=[1.03 ; 1.25]), for lung cancer (SMR = 1.51; 95%CI = [1.25 ; 1.79]) and for silicosis (SMR = 6.02, CI95%=[3.68 ; 9.30]) among the French miners. No excess is observed here for all cancers after exclusion of lung cancers. An excess of death from larynx cancer as observed in the first analysis in 1993 [Tirmarche 1993] is not confirmed in the present cohort (SMR = 1.18; CI95% = [0.75 ; 1.75]) [Laurier 2003]. Among the Czech miners, all cancers, lung cancers, all cancers except lung cancer, and leukemias (all types) occurred more often than expected. Like in the French cohort, mortality from larynx cancer was not elevated. The number of respiratory diseases, circulatory diseases, and external causes were elevated in the Czech, but not in the French cohort.

In Table WP1.7, no SMRs are given for silicosis, since silicosis does not occur in the general population, but only in occupationally heavily exposed populations. Thus, the value for the general population reflects the industries of the area the population was taken from. With this qualification, the observed 20 cases of silicosis in the French cohort are 6 times what would be expected, while the 10 cases in the Czech cohort are 2.5 times what would be expected.

For the German cohort, only a few SMR values could be calculated. This is due to the late stop of field work. All of the given SMRs (i.e. for all cancers, lung cancer, all cancers except lung cancer, leukaemia, and laryngeal cancer) are below 1, but in no case is it statistically significant.

Table WP1.7: Observed (O), Expected (E) death and Standardized Mortality Ratio (SMR) for selected causes of death, by cohort

	France		Czech Republic		Germany	
	O/E	SMR	O/E	SMR	O/E	SMR
Mortality from		95%CI		95%CI		95%CI
All causes	1162/1099.4	1.06 0.99 – 1.12	1871/1325.3	1.41 1.35 – 1.48	639/n.a.	n.a.
All cancers	395 / 347.8	1.14 1.03 – 1.25	709 / 351.2	2.02 1.87 – 2.17	87 / 101.8	0.85 0.68 – 1.05
Lung cancer	126 / 83.1	1.51 1.25 – 1.79	449 / 119.6	3.75 3.41 – 4.12	18 / 19.24	0.94 0.55 – 1.48
Leukaemia	14 / 9.7	1.43 0.79 – 2.43	16 / 9.6	1.67 1.05 – 2.54	5 / 7.22	0.69 0.27 – 1.45
Larynx cancer	24 / 20.4	1.18 0.75 – 1.75	12 / 8.6	1.39 0.80 – 2.25	1 / 1.50	0.67 0.02 – 3.14
Bone cancer	3 / 2.8	1.08 0.22 – 3.15	4 / 2.3	1.75 0.59 – 4.00	n.a.	
all cancers excl. lung	269 / 264.1	1.02 0.90 – 1.10	260 / 231.6	1.12 1.01 – 1.24	69 / 82.6	0.84 0.65 – 1.06
Respiratory disease	54 / 50.5	1.07 0.80 – 1.39	99 / 82.1	1.21 1.01 – 1.42	n.a.	
Circulatory disease	251 / 269.1	0.93 0.82 – 1.06	664 / 583.2	1.14 1.07 – 1.21	n.a.	
External causes	176 / 158.2	1.11 0.95 – 1.29	215 / 143.5	1.50 1.33 – 1.68	n.a.	
Missing causes	66 (5.7%)		8 (0.4%)		82 (12.8%)	

n.a.: not available

5.2 Mortality from lung cancer

Figures WP1.6, WP1.7 and WP1.8 show the rate of lung cancer death per 10 000 person-years by age, calendar year and year of birth for French and Czech cohorts. This is given only for the French and Czech cohort, since for the German cohort, the number of cases is too small. The rate of lung cancer is higher in the Czech cohort. The trend according to calendar year show that lung cancer deaths appear earlier in the Czech cohort.

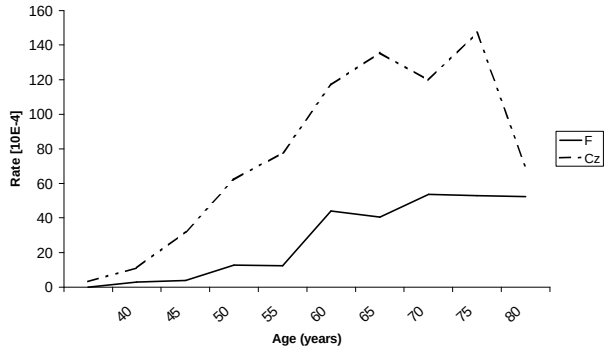

Fig. WP1.6: Lung cancer death rate (per 10 000 PY) by attained age and cohort

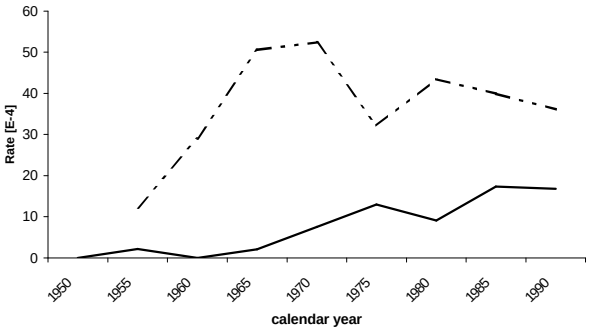

Fig. WP1.7: Lung cancer death rate (per 10 000 PY) by calendar year and cohort

Fig. WP1.8: Lung cancer death rate (per 10 000 PY) by year of birth and cohort

5. STATISTICAL ANALYSIS OF LUNG CANCER RISK ASSOCIATED WITH RADON EXPOSURE

The German cohort is young, and subsequently the number of observed deaths is small. Especially for lung cancer, only 18 have been observed. This number is too small to conduct sophisticated dose-response analyses. Thus, the statistical analysis of lung cancer risk associated with radon exposure has only been done for the French and the Czech cohorts.

5.1 General description of statistical analysis

Analyses are based on the excess relative risk models, where the risk of lung cancer is the product of baseline risk and relative risk. In general, the size of baseline risk is proportional to person-years, and background risks (rates) are internally estimated accordingly to the fitted model (internal approach) [Breslow and Day 1987]. Alternatively, the size of baseline risk can be assumed to depend on expected numbers that are derived from person-years and national mortality data (external approach). In both approaches, baseline rates are estimated for each level of strata defined by age, calendar year and birth cohort. The external approach makes use of age specific mortality in the general population, although national and cohort rates are not assumed to be equal. In analyses of the French cohort, the internal approach was used, whereas in analyses of the Czech and of the joint cohorts a stratified external approach was used, described elsewhere [Tomášek 2002]. This different approach in the Czech cohort was used because only very few cases were exposed to low levels of exposure and

majority of cases were from high exposures making difficult to estimate correctly background rates corresponding to zero exposure. For the joint analyses, stratification by country is added. The general form of the model is [Thomas 1983, Hastie and Tibshirani 1993]:

$$l(t,w,z) = l_0(t)\, f(t,w,z) \qquad \text{Eq WP1.1}$$

where $f(t,w,z)$ is the relative risk, $l_0(t)$ is the mortality rate among non-exposed, $w(t)$ is the cumulative radon exposure at time t, and $z(t)$ are time-dependent modifying factors of the exposure-response relation. Two different forms of $f(t,w,z)$ are used to take into account the effect of z. First, a continuous function of the modifying factors leads to:

$$f(t,w,z) = 1 + b\, w(t)\, \exp(a\, z(t)) \qquad \text{Eq WP1.2}$$

where b is a parameter measuring a unit increase in excess relative risk per unit of exposure (ERR/WLM), and a measure the impact of the modifying factors on b. Using this method, impact of following modifying factors is tested: age, age and time when half of the exposure was received.
The second approach consists in dividing the exposure among various time dependent windows, and then building a piecewise constant function over these 'windows' [Lubin 1994]. The influence of the modifying factors is examined by significant change in risks for J fixed levels of the factors. The relative risk function can be written:

$$f(t,w,z) = 1 + b \sum_j q_j\, w_j(t) \qquad \text{Eq WP1.3}$$

with $\sum_j w_j(t) = w(t)$, where $w_j(t)$ is a time window of exposure for the j*th* level of the factor z ; q_j represents the relative contribution to the risk specific for level j of the factor. Using this method, impact of the following modifying factors is tested: method of exposure assessment and exposure rate based on annual exposure data. In the method of exposure assessment windows, exposures based on measurements contributed to cumulative measured exposure and estimated or extrapolated exposures contributed to cumulative estimated exposure.

In order to take into account several modifying factors in the same model, a mixture of both methods are used [Tomášek 1994]. All these models are nested in the simple model having no modifying factors, which is denoted by M1. For comparison, a version of the BEIRVI-age-concentration model was fitted to the French and Czech cohort, using firstly the same structure and stratification and secondly putting an additional parameter for estimated exposure [BEIR VI 1999]. The evaluation of exposure rate was based on annual exposure windows, rather than on average exposure rates as in BEIR VI. In the present approach, contributions of annual exposures to cumulative exposure were differentiated according to annual exposure rates in categories: <0.5 WL, 0.5-1 WL, 1-2 WL, 2-4 WL, >4 WL.
The modification of exposure-response relationship by age, time since exposure, and age at exposure was studied using continuous variables rather than categorical variables. The reasons for using the continuous approach were (1) lower number of estimated parameters in comparison to categorical approach and (2) the same treatment of modifying effect of age, time since exposure, and age at exposure. The age at exposure and time since exposure were defined by the time when half of the current 5-year lagged exposure was attained [Ševc 1993, Tomášek 2002]. The two variables are denoted by AME (age at median exposure) and TME (time since median exposure), respectively. The above approach was preferred rather than approaches issuing from first or last exposure, as such approaches do not reflect properly the cardinal contributions of annual exposures that were usually higher in early years.

The Poisson regression was used to fit these models, so information on exposure was grouped. Person-years were created using DATAB module of Epicure [Preston 1996] for the French study, and using a separate program for the Czech study. Person-years have been cross-classified by age (<40, 40-49, 50-59, 60-69, >70 years), calendar period (<1965, 1965-74, 1975-84, 1985-95), birth year (<1900; 1900-09; 1910-19; 1920-29; 1930-30; 1940-49; 1950-59; 1960-69) and cumulative exposure (0, 0-9, 10-49, 50-99, 100-199, ≥200 WLM). Additional cross-classification was needed to take into account modifying factors. A five-year lag interval was considered between exposure and risk. Maximum

likelihood parameter estimates and likelihood ratio tests for nested models were obtained using AMFIT module of Epicure for both studies. Confidence intervals are likelihood based. For the joint analysis, results were reproduced using firstly Czech program and AMFIT, secondly using DATAB and AMFIT. For all fitted models, background rates in age groups were tabulated in order to compare background and nationally expected numbers.

5.2 Results from Statistical analysis by cohort

Table WP1-8 shows the results from analyses of the simple model with both cohorts, of model with windows for estimated and measured exposure, and of the modifying effect of age, age at exposure, and time since exposure.

French cohort

A significant excess relative risk is estimated from Model 1 (b =0.008 95%CI: [0.003 - 0.014]). The method of exposure assessment has a great impact on the estimation of the risk: estimated ERR/WLM is 8 times higher for measured exposure (b_M = 0.024; 95%CI: [0.006 - 0.038]) than for estimated (b_E = 0.003; 95%CI: [-0.002 - 0.008]). Attained age, age at median exposure and time since median exposure show no significant effect. Earlier published results showed that windows according to age at exposure do not significantly improve the fit, but showed a significant decreasing in risk with time since exposure windows: risk is significant only for the exposure received 5 to 14 years earlier. The significant effect of exposure rate disappeared when method of exposure assessment windows are used [Rogel 2002].

Czech cohort

Models of relative risk fitted in the Czech sub-cohort confirmed results published earlier for this sub-cohort of 5002 miners [Tomášek 1999, Tomášek 2002]. The modifying effects of time since exposure (TME) and age at exposure (AME) were both significant (Table WP1.8). In addition, it was analysed if exposures based on estimates or extrapolations are different from those based on direct radon measurements. The ERR/WLM for estimated exposure was 61% in comparison to measured exposures. However, the difference was not statistically significant (p=0.35), partly because the proportion of estimated exposures was relatively low (7%). The question of the inverse exposure rate effect was analysed using exposure windows described above but only in four exposure rate windows (0-1WL, 1-2WL, 2-4WL, and >4WL) as there were insufficient numbers of cases at low exposure rates. In the Czech cohort, no major differences in exposure rate specific ERR/WLM were observed (p=0.10) and the results in terms of ERR/WLM were practically identical with adjustment for method of exposure assessment (p=0.97) and when additional adjustment for time since exposure and age at exposure (p=0.85).

Table WP1.8: Results from models with cumulative exposure *(W)*, and from models with windows for method of exposure assessment (measured*:W_M*, estimated *:W_E)*, and using continuous modifying factor of age *(AGE)*, age at median exposure *(AME)* and time since median exposure *(TME)*

		Estimate per 100WLM, 95%CI, difference in deviance with M1 (df)								
Model	Var.	French cohort N=5098			Czech cohort N=5002			Joint French and Czech N=10100		
M1	W	0.7	0.2 – 1.4		3.6	1.9 – 8.5		1.6	1.1 – 2.5	
M2	W_M	2.4	1.1 – 4.6	10.0 (1)	3.8	1.9 – 8.8	0.9 (1)	2.8	1.8 – 4.5	19.2 (1)
	W_E	0.2	-0.1 - 0.9		2.3	0.0 – 7.6		0.4	-0.1 – 1.1	
M3[a]	W_M	4.3	1.3 – 11.2	11.8 (2)	5.3	2.8 – 11.0	9.9 (2)	4.9	2.9 – 8.3	32.1 (2)
	W_E	0.7	-0.1 – 2.7		2.6	-0.2 – 9.3		0.9	0.1 – 2.7	
	AGE	0.54	0.23 - 1.27		0.47	0.28 - 0.77		0.46	0.30 - 0.71	
M4[b]	W_M	4.8	1.5 – 12.5	12.6 (3)	4.8	2.5 – 10.3	10.5 (3)	4.5	2.7 – 7.6	32.1 (3)
	W_E	0.6	-0.1 – 2.4		2.0	-0.2 – 8.0		0.9	0.1 – 2.5	
	AME	0.42	0.15 - 1.19		0.54	0.32 - 0.91		0.51	0.33 - 0.81	
	TME	0.58	0.24 - 1.41		0.44	0.26 - 0.75		0.46	0.29 - 0.71	

[a] estimates for a mean age of 50 years old, modification of age by decade
[b] estimates for a mean AME of 30 years old and a mean TME of 20, modification of AME and TME by decade

5.2 Results from joint analysis of French and Czech cohorts

Several models were fitted in the joint French and Czech studies. Table WP1.8 shows the results of the simple constant relative risk model (M1), the model with exposure windows for method of exposure assessment (M2), and the preferred model with continuous modification by time since exposure and age at exposure (M4). The model with attained age modifier (M3) was fitted for comparison. In terms of deviance, models M3 and M4 are very similar, particularly because the relative modifying effect of age at exposure (0.51 per decade) and time since exposure (0.46 per decade) were very close. Both modifying factors were significant in the joint study and the shape of dependence was similar in both studies. In addition, estimated age specific background rates for models M3 and M4 (not shown) were in line with mortality from other diseases in both studies and with lung cancer rates at low exposures (<20WLM) in the joint study. Figure W1.9 gives a graphical representation of the impact of the modifying effect of age at exposure and time since exposure on ERR/WLM when estimated from model M4. Figure WP1.9 summarises values of relative risk according to level of cumulative exposure estimated from Model M4 when different pattern of AME and TME are encountered and shows that model M4 predict no effect of exposure rate.

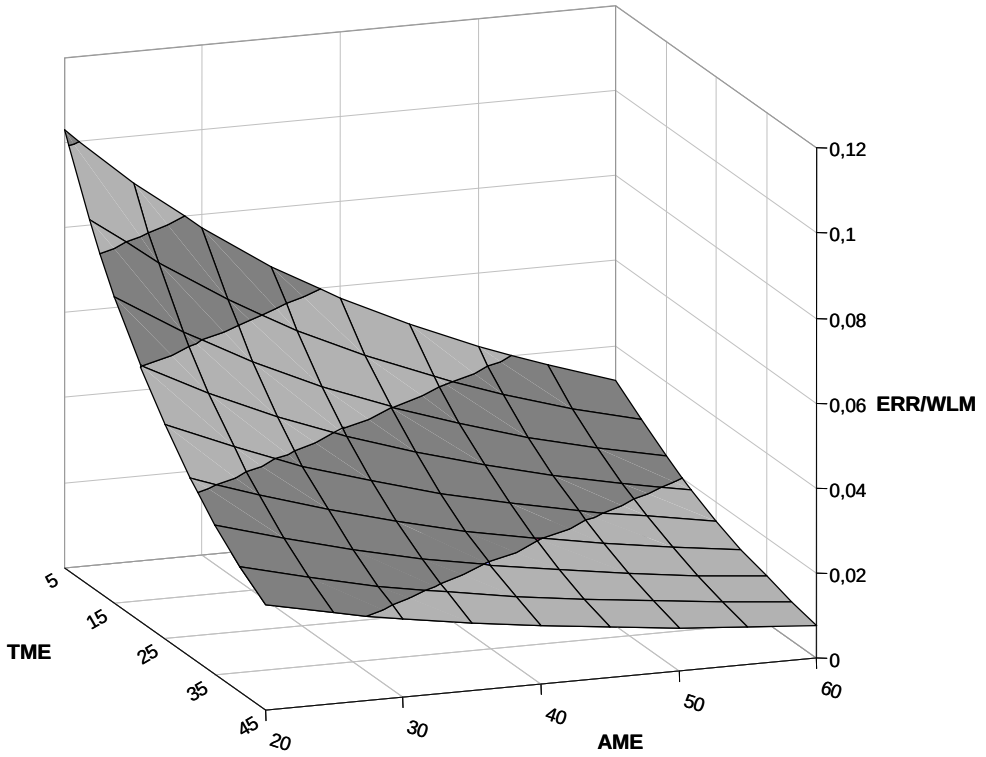

Fig. WP1.8: Excess Relative Risk per WLM by age at median exposure (AME) and time since median exposure (TME) from estimation of Model M4, using the joint French and Czech cohort and the coefficient for measured exposure.

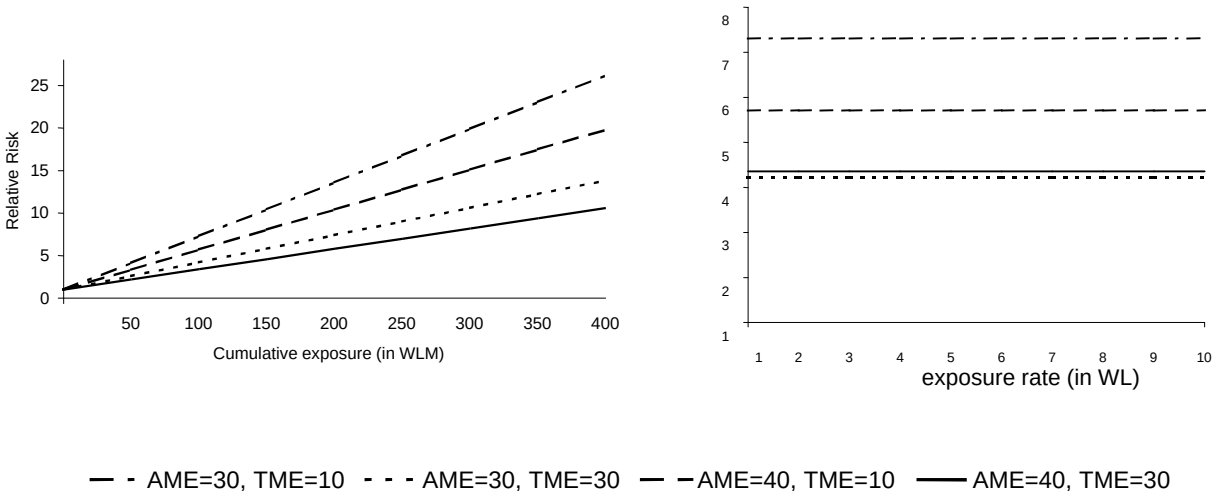

Fig. WP1.9: Relative risk by cumulative exposure (left panel), and relative risk at 100 WLM by exposure rate (right panel), using Model M4 estimates based on the joint French and Czech cohort, with different mean age at median exposure (AME) and mean time since median exposure (TME). The coefficient for measured exposure is used.

The analysis of exposure rate effect using exposure windows (Table WP1.9) was conducted only in the joint study, as lower numbers of cases in separate studies did not allow to fit models with so many

exposure windows. When only 5 exposure rate windows were used, significant differences were observed between exposure rate specific ERR/WLM, primarily due to the last category. However, this difference was not seen, when adjustment for method of exposure assessment was added to the model. In comparison, models M6 and M2 were not statistically different (p=0.54), neither models M7 and M4 (p=0.47). In conclusion, exposure rate was not a significant modifying factor at exposures in both studies.

Table WP1.9: Analyses of exposure rate. Results from models with windows of method of exposure assessment (Measured, Estimated) and annual rate of exposure (rate), and using continuous factor of age at median exposure (AME) and time since median exposure (TME)

		Estimates per 100 WLM, 95%CI, difference in deviance with M1 (df)		
		Joint French and Czech		
Model	Variable	N=10 100		
M1	W	1.6	1.1 - 0.025	
M5	Wrate < 0.5	3.7	1.5 – 7.1	28.8 (4)
	Wrate 0.5-1	1.3	0.0 – 3.4	
	Wrate 1-2	2.6	1.5 – 4.4	
	Wrate 2-4	2.6	1.4 – 4.4	
	Wrate >4	0.6	0.0 – 1.4	
M6	$W_{M,}$ rate < 0.5,	3.9	1.7 – 7.2	35.3 (5)[b]
	$W_{M,}$ rate 0.5-1	1.4	-0.0 – 3.5	
	$W_{M,}$ rate 1-2	2.9	1.6 – 4.9	
	$W_{M,}$ rate 2-4	2.5	1.3 – 4.3	
	$W_{M,}$ rate >4	2.0	0.1 – 5.1	
	W_E	0.4	-0.0 – 1.1	
M7 [a]	$W_{M,}$ rate < 0.5	6.0	2.5 – 12.2	46.2 (7)[c]
	$W_{M,}$ rate 0.5-1	1.8	-0.3 – 5.4	
	$W_{M,}$ rate 1-2	4.2	2.2 – 7.6	
	$W_{M,}$ rate 2-4	4.0	2.1 – 7.3	
	$W_{M,}$ rate >4	3.1	0.2 – 8.1	
	WE	0.9	0.1 – 2.4	
	AME	0.51	0.33 - 0.81	
	TME	0.46	0.29 - 0.71	

[a] estimates for a mean AME of 30 years old and a mean TME of 20, modification of AME and TME by decade
[b] difference in Deviance of M6 with M2 : 3.09 with 4 df
[c] difference in Deviance of M7 with M4 : 3.56 with 4 df

Table WP1.10 provide results for comparison of the BEIR VI preferred model. In contrast to BEIR VI-age-concentration model, results from the joint French and Czech studies did not confirm the inverse exposure rate effect (based on mean exposure rate). In addition, the modification by categorical attained age in the joint cohort was different from BEIR VI preferred model. Nevertheless, the continuous modification estimated from model M3 in the joint study provided a decrease consistent with BEIR VI models.

Table WP1.10: Results from models having the same structure and same stratification as BEIR VI-TSExposure-age-concentration model [BEIR VI 1999]. Note that rate is here calculated as a mean exposure rate

		11 cohorts-study (n=60570)	French and Czech cohorts (n=10100)	
Model	Variable	BEIRVI-concentration estimates[a]	Estimates [95%CI] using BEIR VI model	Estimates [95%CI] using adapted BEIR VI model[b]
M8	W[c]	7.68	7.81 [3.21 – 15.2]	5.35[c] [2.03 – 12.1]
	TSE[5-15[	1.00	1.00	1.00
	TSE[15-25[	0.78	0.61 [0.39 - 0.94]	0.63 [0.35 - 0.94]
	TSE>25	0.51	0.34 [0.19 - 0.55]	0.31 [0.17 - 0.52]
	age<55	1.00	1.00	1.00
	age 55-64[	0.57	0.32 [0.14 - 0.76]	0.35 [0.15 - 0.80]
	age 65-74	0.29	0.46 [0.17 - 1.26]	0.58 [0.22 - 1.51]
	age>75	0.09	0.50 [0.07 - 3.42]	0.77 [0.13 - 4.61]
	rate<0.5	1.00	1.00	1.00
	rate[0.5-1[	0.49	0.77 [0.45 - 1.34]	0.91 [0.49 - 1.71]
	rate[1-3[	0.37	0.91 [0.54 - 1.52]	1.10 [0.60 - 1.99]
	rate[3-5[	0.32	0.56 [0.22 - 1.38]	0.54 [0.19 - 1.59]
	rate[5-15[	0.17	0.60 [0.12 - 2.94]	/
	rate>15	0.11	/	/

[a] as published in BEIR VI 1999, p82 table 3-3
[b] parameter for Measured exposure
[c] estimates per 100 WLM

6. DISCUSSION

6.1 Data, exposure and mortality

The data of the three cohorts are of comparable quality. In terms of follow-up and ascertainment of causes of deaths, the methods are pretty much alike. In all cases, administrative files are primarily used and the loss to follow-up is very low. Of course, the length of follow-up varies between the cohorts, since for the French and in the Czech study the inclusion criteria allowed for an earlier time of first employment than in the German cohort. It has to be mentioned that the percentage of unknown causes of death varies largely between the cohorts. While it is only 0.4% for the Czech miners, it is 5.7% for the French and 12.8% for the German miners, respectively. Especially for the German cohort, there should be further efforts to lower this percentage.

In terms of exposure to radon and its progeny, the mean values for the three cohorts differ by a factor of 5. For those who were actually exposed it is lowest in German, highest in Czech, and intermediate in French miners. While there are no unexposed individuals in the Czech cohort, the respective percentage is 18.6% and 15.8% in the French and in the German cohort, respectively.

There are differences in mortality between the cohorts. 37.4% of the Czech cohort are deceased. The figures for France and Germany are 22.8% and 3.7%, respectively. Again, it becomes obvious that the German cohort is by far younger than the others. For this cohort, none of the SMRs is elevated. Considering the French and the Czech cohort, the overall mortality is elevated only in the latter. Nonetheless, with respect to SMRs for single causes of death they are comparable. For lung cancer, both cohorts reveal significantly increased rates. For all cancers excluding lung cancer, the SMR is significantly elevated in the Czech miners, but close to unity for the French cohort. Model assumptions are indicative for an increased risk for leukaemia and larynx cancer [Jacobi 1995].

Neither study reveals an increased risk compared to the general public, but for the French and Czech cohort the SMR values are above 1. Adding the observed and expected numbers of cases from the three cohorts, the combined SMR values turn out as follows: leukaemia 1.31 [0.81;2.01], laryngeal cancer 1.21 [0.85;1.67]. This could be indicative of a slightly increased risk for the two cancer sites, but further analyses are necessary to confirm this.

Information on causes of death other than cancer is only available for the French and the Czech cohort. The number of cases for respiratory and circulatory diseases and for external causes is elevated among the Czech but not the French miners. The number of deaths due to silicosis is elevated in both cohorts, but the baseline rate itself is influenced by occupational conditions. Overall, a detailed exposure-risk analysis has to be carried out for all causes other than lung cancer. To achieve that, a further follow-up is necessary to broaden the database.

6.2 Results from statistical analysis

The evaluation of exposure rate was based on annual exposure windows, rather than on average exposure rates as in BEIR VI (calculated as the ratio of cumulative exposure and total months worked). In the BEIR VI approach, the effect from high exposure rates (mostly in early years of mining) is confounded by much lower exposure rates in later periods of mining. In the present approach, contributions of annual exposures to cumulative exposure were differentiated according to annual exposure rates in categories: <0.5WL, 0.5-1WL, 1-2WL, 2-4WL, >4WL. Although the inverse exposure rate effect was demonstrated in many studies of miners [Lubin 1994], results from the present study suggest that exposure rate influence on the risk cannot been demonstrated at rates below 50 WLM/y. The absence of exposure rate effect was reported in BEIR VI at low cumulative exposures (<100 WLM). The present results suggest that the reduction of the ERR/WLM cannot be expected even at relatively high exposure of 400 WLM corresponding for instance to a chronic 10 year exposure at mean exposure rates in early years of the present study.

The exposure windows approach used to evaluate differences in ERR/WLM from exposures based on direct measurements and exposures based on estimated or extrapolated exposures clearly demonstrated the importance of exposure data quality and measurement errors in the first years of exposure. If the method of exposure assessment is not taken into account, the risk coefficients are substantially underestimated (in the French study by a factor of 3.4 and in the joint study by a factor of 1.8).

The modification by attained age, time since exposure and age at exposure was evaluated in the present study using continuous approach. As attained age is the sum of age at exposure and time since exposure, the adequate evaluation of time since exposure or age at exposure should not be based on models in which attained age is present. In the present model (M4), the effect of age at exposure and time since exposure were similar (roughly 0.5 per decade) in both studies separately. Only in case of such a similarity, the use of attained age as the only modifying factor is justified.

The choice of model M4 as preferred model is supported by the estimated age specific background rates corresponding to the model. Trends in background mortality are in line with mortality from other diseases in both studies and with lung cancer rates at low exposures (<20WLM) in the joint study. All these age specific mortality exhibit lower SMR in comparison to national rates for younger age groups and higher SMR for age groups over 60.

In comparison to the BEIR VI-exposure-age-concentration model, the present preferred model (M4) predicts higher relative risk in ages below age 50, particularly because the relative risk from exposures received at younger ages (<35 years) is substantially higher than that from the BEIR VI, as illustrated in Figure WP1.10. In both models, the decrease of relative risk by attained age and/or time since exposure is similar for exposures received at older age. For exposures received at younger age, the risk predicted by the present model is somewhat higher than that from the BEIR VI-concentration model. Generally, the decrease by attained age and/or time since exposure (in 2 parameters) seems to be described better by a continuous variables than by a combination of time since exposure window and categories of attained age (in 5 parameters) used in BEIR VI models.

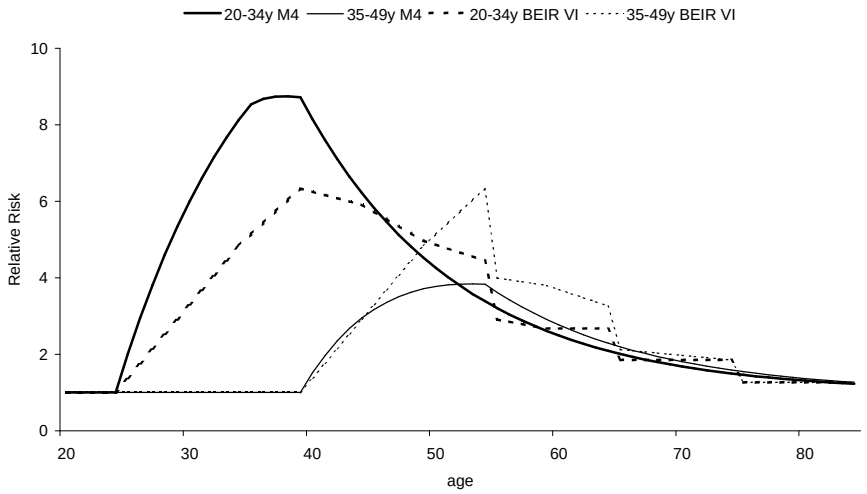

Fig. WP1.10: Relative risk from exposures 90 WLM received at ages 20-34 (thick) and 35-49 (thin) – comparison of results from the BEIR VI-age-concentration model (dashed lines) and the preferred model (M4) from the joint study (solid lines)

7. PERSPECTIVES

The basic perspective for the German cohort is a continuation of the follow-up to increase the number of cases and have a better basis for risk estimates [Kreuzer 1999]. Furthermore, SMR analyses will be completed to be fully comparable to those from France and the Czech Republic. On a broader number of cases it will be possible to conduct ERR analyses. Given the large group of individuals with low exposures, this will be a good and homogenous group to derive reliable results. With respect to the number of unknown causes of death, which is due to the fact that death certificates are normally destroyed ten years after death, newly developed mechanisms will be used to improve the situation [Klug 2003]. Nonetheless, forthcoming analyses will employ statistical methods for handling missing causes of death [Rittgen 2000].

Results from the SMR analyses are indicative for an increased risk from lung cancer. The numbers of leukemias and larynx cancers are non-significantly elevated, when all three cohorts are considered. Taking data from the French and Czech cohort only, for which there is a sufficiently long follow-up, the SMR for leukaemia is 1.55 (95%CI: 1.05 - 2.22). Thus, leukaemia mortality should be analysed in more detail using ERR models [Laurier 2001]. Probably, nested case-control studies might be worthwhile to include information on other sources of radiation, too, e.g. medical examinations during the employment period. Next to that, underground exposure to inhaled uranium dust and gamma radiation might play an important role and should be considered in respective cohort analyses. For laryngeal cancer, further follow-up is needed to clarify the validity of the small increased risk, if at all.

In all three studies, it can be expected that longer follow-up will contribute to an adequate and more powerful estimation of the effect of time since exposure, using flexible tools such as B-splines [Hauptmann 2001]. The follow-up of the French cohort has been extended to 1999. Descriptive analysis will soon be performed. Confirmation of the strong effect of method of exposure assessment in that cohort has to be studied, and models allowing measurement errors will be considered. For subcohorts exposed to low levels, cases observed in extended follow-up are of importance, particularly in the correct estimation of background lung cancer rates.

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WORK-PACKAGE 2: NESTED CASE-CONTROL STUDIES

Principal contractor: IRSN, D. Laurier
Participants: IRSN (S. Billon, D. Bergot), BfS (B. Grosche, G. Hammer), NRPI (L. Tomasek)

WORK-PACKAGE 3: COMBINED ANALYSIS OF OCCUPATIONAL AND INDOOR EXPOSURE

Principal contractor: GSF, I. Brüske-Hohlfeld
Participants: GSF (A. Schaffrath-Rosario, H.E. Wichmann)

OBJECTIVES

A major drawback of cohort data is the lack of information on some important risk factors for lung cancer that may confound or modify the estimated relationship between radon and lung cancer risk. A major risk factor, that has certainly to be taken into account, is tobacco consumption, but other risk factors may also be of interest (e.g. indoor radon exposure of the miners and previous professional exposures to potential carcinogenic substances). Nevertheless, such data are generally missing or sparse among miners' cohorts, and the collection of information for the whole population would have been a huge task.

A solution to this problem was to perform case-control studies nested in the cohorts. This approach relies on the analysis of data collected retrospectively on a subset of individuals selected from the cohort: the cases (miners deceased from lung cancer) and controls (miners of the same cohort, with similar characteristics for age, period of birth… but free of lung cancer). It allows the estimation of relative risks and interactions between risk factors, and the effort for data collection is focused on a much smaller subset than the complete cohort.

The goal of WP2 was to conduct case-control studies within the French, German and Czech cohorts of uranium miners. The study design in each country was adapted to the available sources of data. Regular meetings allowed discussing the protocols and developing a common method of data collection, like:

- Finalization of the protocol,
- Definition of inclusion criteria for the study population,
- Selection of cases and controls,
- Evaluation of possible data sources in regard to availability and completeness,
- Data collection,
- Statistical analysis of the data.

One goal of WP3 was to analyse the lung cancer risk of former uranium workers of the German Wismut company on the basis of a case-control study data set. This task was very similar to those of WP2, and the results are presented jointly with those from WP2. The final aim of WP3 was the combined analysis of occupational and indoor exposure. The necessary fieldwork covered the measurement of indoor radon in homes of cases and controls by applying glass surface detectors and the evaluation of silicosis (according to the classification of the International Labour Organisation - ILO-classification) among miners with and without lung cancer. The results regarding these specific points are presented below.

1. DEFINITION OF THE STUDY POPULATION

- **French study :**

Source population:
All subjects are part of the French cohort of uranium miners (N=5098, see details in WP1). Based on results from the feasibility study that has been conducted during the EC 4th Framework Programme,

the population was limited to miners alive in 1980, in order to exclude inquiries too far in the past. The period of inclusion is therefore from 1980 to 1994.

Selection criteria of the cases:
In the cohort, 125 miners died from lung cancer, among which 88 died in the period 1980-1994. Nevertheless, in the cohort, causes of death relied essentially on the principle cause of death according to the death certificate. When considering other sources of information on causes of death (associated cause of death from the death certificate and information from the Occupational Medical Service of COGEMA), 12 additional cases were identified as lung cancer. The study therefore includes a total of 100 lung cancer cases.

Selection criteria of the controls:
Controls were selected from the same cohort of miners. For each case, controls were matched according to birth date (same 5-years period as the case birth date) and attained age (still alive at the time of the case death). The matching rate was 1:5. The selection was performed in two steps: (i) selection of all eligible controls for a case (the number of possible controls per case ranged from 6 to 693), (ii) random selection of 5 controls among the subset of all possible controls for each case. This approach, classical for nested case-control studies [Breslow 1983], allows the selection of cases among controls (a case can be an eligible control for another case if he meets the matching criteria: it happened 14 times) and also the selection of the same control for different cases (62 subjects).

Study population:
Finally, the study includes a total of 600 subjects (100 cases and 500 controls). As certain miners have been selected more than once, the total file includes in fact 515 different individuals.

- **Czech study :**

Source population:
All subjects are part of the Czech cohort of U-miners (N=5002, see details in WP1), diagnosed after 1960. The period of inclusion is from 1961 to 2002. The Czech cohort is composed of two sub-cohorts: sub-cohort S (2552 miners) employed in the region of Jachymov and sub-cohort N (2450 miners) employed in the region of Pribram, and for whom information about smoking are available for 85%.

Selection criteria of the cases:
In the cohort, 488 miners died from lung cancer before age 85. Lung cancers as a death cause were identified at local registries of death or at the Department of occupational medicine in Pribram. Cases are miners deceased from lung cancer in the period 1961-2002, for whom information on smoking status were available. Without smoking selection criteria, there are 488 possible cases and 1464 possible controls, so a total of 1952 individuals.

Selection criteria of the controls:
Controls have been selected within strata defined by year of birth (5y) on condition being alive when the case died. The matching rate was 1:3.

Study population:
The study population consisted in 1009 individuals, that is 320 cases and 689 controls.

- **German study (WP2) :**

Source population:
Unlike in WP1, cases were taken from the entire cohort. The number of cases from sub-cohort C, which is considered in WP1, didn’t exceed 18.

Cases had to be known as having died from lung cancer from the follow-up as of Dec. 2001. Controls were randomly selected from those cohort members for whom the definitive information was available at the end of Dec. 2001.
Based on results from the feasibility study that has been conducted during the FP4, only miners born 1. Jan 1927 or later were used as data base. Thus, the number of eligible miners was 42 955 from the overall cohort of 58 619.

Selection criteria of the cases:
The cases are all the miners deceased, with lung cancer as the cause of death, born after 1926, and not included in the pilot study. 706 cases were included.

Selection criteria of the controls:
Two controls were selected per case, matched by year of birth. A control had to be alive at the time of death of the respective case. The final number of controls is 1412. The matching rate was 1:2.

Study population:
The study population included 706 cases and 1412 controls.
Like in the French study, some of the cases were also controls and some of the controls were controls for more than one case. Subsequently, the study population consisted of 2001 individuals. Information additional to that known from the cohort study was taken from a) mailed questionnaires to either alive participants or next-of-kin, whatever was applicable, and b) from the files of the Wismut Health Archive.
The following figures are based on the final case-control set rather than on individuals, since some could be both case and control. The response rate among the cases and controls was 44%, with 37.8% among the cases and 47.7% among the controls. The higher response among the controls compared to the cases seems to be due to the fact that among the controls 80% were alive, whereas all cases were deceased, of course. The total number of questionnaires for cases and controls is 267 and 666, respectively. There are two shortcomings. First, the data from the health archive could not be computerized in time and subsequently could not be used in the data analysis. Second, the exposure estimates have to be considered as preliminary for the years until 1961. It was only shortly before the end of the project that more reliable estimates were available. Thus, no risk estimates can be given in this report but will be calculated later.

- **German study (WP3) :**

Source population:
All subjects, cases and controls, were male residents of Thuringia or Saxony. They had been employed underground at the uranium mines of the Wismut-Company at some time between 1946-1990. There was no age restriction. Cases were recruited from 5 study clinics (Gera, Chemnitz, Coswig, Bad Berka, Zschardrass) between 1991-1999. The response rate was 73%. Controls had participated at least once in the medical health care surveillance system (“Zentral Betreuung Wismut” ZeBWis) for former Wismut workers. 29 % of the eligible workers were willing to participate in the study.
Subjects included in WP3 are not necessarily part of the German nested case-control study in WP2, but were incident cases rather than deceased cases as in WP2.

Selection criteria of the cases:
The cases had a diagnosis of primary lung tumour (no tumour recurrence or metastasis of another tumour), not older than 6 months, which was histologically or cytologically ascertained. 584 cases were included.

Selection criteria of the controls:
A total of 1172 controls were included, matched according to date of birth of cases in five year intervals and according to region. The matching rate was 1:2.

Study population:
A total of 1756 individuals were interviewed. Several subjects had to be excluded because they did not fulfil the inclusion criteria or necessary information was missing or unreliable.
The final study population consisted of 1586 subjects, 507 cases and 1079 controls.

Overlap among the German studies (WP1, WP2, WP3)
Based on information on date of birth and employment period, it could be assessed that among the 507 cases of the case-control study in WP3, 55 subjects were included in the nested case-control study of WP2. It is not necessarily so that the cases of WP3 are cases in WP2, too, since the inclusion criteria and the recruitment periods differ. 56 subjects of the nested case-control study (WP2) are also members of the German cohort in WP1, while no one from the case-control study (WP3) is included there.

Table WP2.1 summarises the design of the four case-control studies.
Description of data for each study is given in tables WP2.2a to WP2.2d. For controls, information are truncated at the date of death (or diagnosis for WP3 study) of the respective case.

Table WP2.1: Study design and description of the population of the four case-control studies

	French study	Czech study	German study (WP2)	German study (WP3)
Base population	French cohort of U miners (N=5098)	Czech cohort of U miners (N=5002)	German Wismut cohort of U miners (N=58 619)	German Wismut case-control study
Selection criteria for lung cancer cases:	death in 1980 – 1994	death in 1960 – 2002 and smoking data	death before 2001 and birth 1927 or later	diagnosis in 1991 – 1999
Matching criteria for controls (identical as respective case):	alive at time of death and period (5y) of birth	alive at time of death, period (5y) of birth and sub-cohort	alive at time of death and year of birth	alive at time of diagnosis, period (5y) of birth and region
Matching rate	1:5	1:3	1:2	1:2
Targeted population	600	1952		4841
Percentage reached	*	52%	**	33%
Number of cases	100	320	706	507
Number of controls	500	689	1412	1079
Number of individuals	515	1009	2001	1586

** Not known as the collection of smoking information is not yet completed.*
*** 40% reached via questionnaires. Information from the Health Archives is available for 100%, but not computerised in time.*

Table WP2.2a: Description of the study population of the French nested case-control study

	Cases (N=100)			Controls (N=500)		
	m	sd	range	m	sd	range
Year of birth	1924	8.3	1901-1951	1924	8.4	1901-1953
Year of death (index y)	1988	3.9	1980-1994	1988	3.9	1980-1994
Age at death (index y)	63.5	7.9	43-85	63.5	7.8	43-85
Year of first employment	1955	5.4	1946-1977	1955	5.9	1945-1981
Age at first employment	30.6	7.6	17.4-53.1	30.9	7.6	16.7-56.7
Year of last employment	1972	11.6	1949-1994	1972	11.7	1948-1994
Age at last employment	48.4	11.4	20.9-62.4	48.8	11.6	20.6-67.0
Duration of employment	18.5	10.8	2-39	18.5	11.4	2-40

m: mean; sd: standard deviation

Table WP2.2b: Description of the study population for the Czech nested case-control study

	Cases (N=320)			Controls (N=689)		
	m	sd	range	m	sd	range
Year of birth	1924	10.4	1896-1952	1927	10.2	1898-1953
Year of death (index y)	1983	10.8	1961-2002	1985	10.2	1960-2002
Age at death (index y)	58.4	9.8	28-84	58.1	9.9	27-82
Year of first employment	1955	6.8	1947-1975	1957	7.6	1941-1975
Age at first employment	30.8	8.0	16-61	30.0	8.1	14-58
Year of last employment	1966	7.5	1954-1989	1966	9.2	1954-1999
Age at last employment	41.9	8.7	20-66	39.3	8.8	20-63
Duration of employment	10.4	4.8	1-28	8.6	5.2	1-34

Table WP2.2c: Description of the study population for the German nested case-control study (WP2)

	Cases (N=706)			Controls (N=1412)		
	m	sd	range	m	sd	range
Year of birth	1932	4.7	1927-1956	1932	4.7	1927-1956
Year of death	1990	6.7	1969-1998	1994*	4.5	1976-2000
Age at death	58.0	7.5	33.8-71.7	63.7*	5.5	45.7-72.3
Year of first employment	1953	6.1	1946-1987	1954	6.3	1946-1985
Age at first employment	21.0	4.0	14.5-47.5	21.8	4.6	14.1-48.9
Year of last employment	1973	13.0	1952-1989	1972	14.4	1949-1989
Age at last employment	41.0	12.9	18.1-62.9	40.4	14.6	17.7-62.9
Duration of employment	19.9	12.9	0.5-42.8	18.6	14.2	0.5-43.4

** N = 267*

Table WP2.2d: Description of the study population for the German case-control study (WP3)

	Cases (N=506)			Controls (N=1075)		
	m	sd	range	m	sd	range
Year of birth	1929	5.4	1912-1947	1929	5.5	1910-1949
Year of diagnosis	1995	2.15	1991-99	1995	2.14	1991-99
Age at diagnosis	66.2	5.61	49-84	66.4	5.87	44-86
Year of first employment	1951	4.6	1946-1972	1952	4.9	1946-1985
Age at first employment	22	4.5	15-41	23	4.7	14-48
Year of last employment	1964	15.3	1947-1996	1965	15.0	1946-1996
Age at last employment	35	14.6	16-68	36	14.9	18-75
Duration of employment	13	13.3	<1-43	13	13.6	<1-43

From the four case-control studies, the total population consists in 1632 cases and 3676 controls, with an average duration of employment varying from 10 to 20 years.

2. RADON EXPOSURE IN THE MINES

Table WP2.3 summarises the sources of information about professional exposures to radon. In all four studies, the exposure data used were the same as the one used in the cohort studies. For controls, exposure was truncated at the date of death of case (WP2) or the date of diagnosis of case (WP3).
The exposure estimates for the German nested case-control study (WP2) are based on a job-exposure matrix, which had to be considered as partly overestimating the real exposure, especially in the years until 1961. An improved version was only available in July 2003. Thus, estimates given in this report on WP2 might be wrong.

Table WP2.3: Sources of information about professional exposures of the four case-control studies

	French study	Czech study	German study (WP2)	German study (WP3)
Source of data	Dosimetric files from COGEMA	JEM based on extensive radon measurements	JEM (old version)	JEM (awaiting new version)
Proportion of missing data	None	None	None	None
Data on exposures other than radon	Gamma rays, ore dust (after 1956)	Gamma, ore dust after 1970	None	Gamma rays, ore dust

The statistical analysis of the Wismut case-control study (WP3) has been finished. The excess relative risk per 100 WLM was much lower than expected by extrapolation from the BEIR VI model. Presently, it cannot be excluded that this very low risk estimate is caused by an invalid JEM that was used for exposure calculation in the study. It was therefore decided to postpone the presentation of data on radon exposure until a second analysis of the data with the upgraded more sophisticated JEM.

Exposure data are presented separately for each study in the following tables WP2.4a to WP2.4c. The average duration of exposure vary from 15 years among the German miners to about 10 years among the Czech miners. The cumulative radon exposure was higher for cases than for controls among the three studies.

Table WP2.4a: Description of exposure data for the French nested case-control study (exposed individuals only)

	Cases (N=88)			Controls (N=378)		
	m	sd	range	m	sd	range
Age first exposure	30.9	7.9	17-50	31.5	7.6	18-54
Age last exposure	44.9	10.6	19-60	44.7	10.6	18-60
Year first exposure	1955	5.3	1946-1977	1957	6.8	1946-1983
Year last exposure	1969	11.2	1949-1993	1970	11.6	1947-1994
Duration of exposure	15.0	10.1	1-35	14.3	10.8	1-37
Time since last exposure	19.6	10.9	1-41	19.0	11.8	1-46
Cumulative radon exposure (WLM) *	93.5	129.3	<1-960.1	63.3	91.7	<1-597.5
Mean rate (WLM/y)	8.4	16.0	<1-110.0	5.0	9.1	<1-110.0

** Up to the date of death of the corresponding case (index year)*

Table WP2.4b: Description of exposure data for the Czech nested case-control study (exposed individuals only)

	Cases (N=320)			Controls (N=689)		
	m	sd	range	m	sd	range
Age first exposure	30.8	8.0	16-61	30.0	8.1	14-58
Age last exposure	41.9	8.7	20-66	39.3	8.8	20-63
Year first exposure	1955	6.8	1947-1975	1957	7.6	1941-1975
Year last exposure	1966	7.5	1954-1989	1966	9.2	1954-1999
Duration of exposure	10.4	4.8	1-27	8.6	5.2	1-34
Time since last exposure	16.6	10.0	0-41	19.0	10.6	0-44
Cumulative radon exposure (WLM) *	153.8	137.7	1-733	89.6	82.2	1-510
Mean rate (WLM/y)	14.3	10.6	0.2-53	11.1	8.7	0.2-56

** Up to the date of death of the corresponding case (index year)*

Table WP2.4c: Description of exposure data for the German nested case-control study (WP2) (exposed individuals only)

	Cases (N=657)			Controls (N=1225)		
	m	sd	range	m	sd	range
Age first exposure	20.9	3.8	14.5-47.5	21.5	4.1	14.1-48.9
Age last exposure	41.4	12.7	18.3-62.9	40.8	14.6	18.3-62.9
Year first exposure	1953	5.9	1946-1985	1953	5.8	1946-1983
Year last exposure	1973	12.9	1952-1989	1973	14.4	1949-1989
Duration of exposure	20.5	12.8	0.5-42.8	19.3	14.2	0.5-43.4
Time since last exposure	16.7	13.8	0-44.2	25.5	14.9	0-49.7
Cumulative radon exposure (WLM) *	731.2	695.9	0.1-2979.7	502.4	622.6	0.1-3331.9
Mean rate (WLM/y)	49.9	55.0	>0-341.0	40.4	54.2	>0-347.5

** Up to the date of death of the corresponding case (index year)*

Cumulative radon exposure, time since last exposure and age at first exposure are presented graphically for French, Czech and German (WP2) studies in Figures WP2.1 to WP2.3. The cumulative radon exposure was higher for cases than for controls in the three case-control studies.

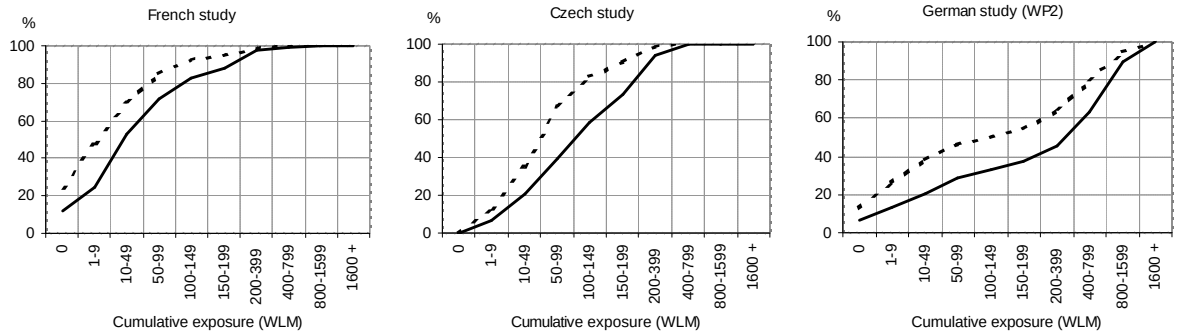

Fig. WP2.1: Cumulative radon exposure in WLM for cases (solid line) and controls (dashed line) for the French, Czech and German nested case-control studies

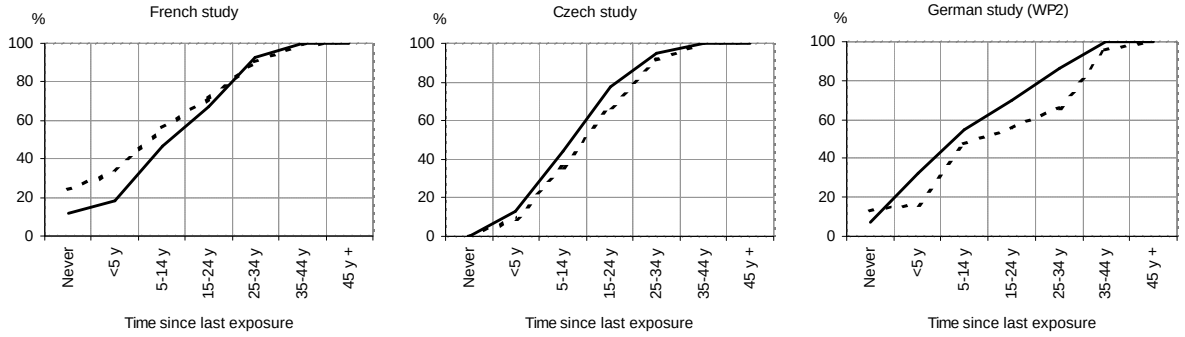

Fig. WP2.2: Time since last exposure for cases (solid line) and controls (dashed line) for the French, Czech and German nested case-control studies

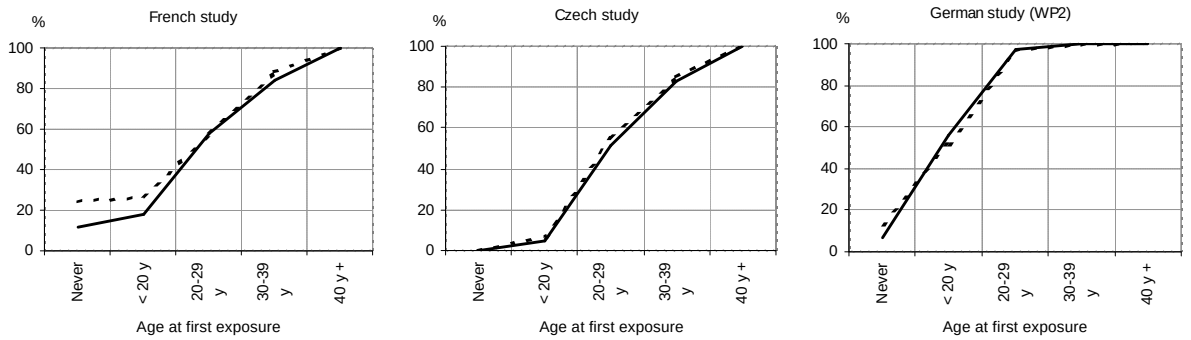

Fig. WP2.3: Age at first exposure for cases (solid line) and controls (dashed line) for the French, Czech and German nested case-control studies

3. INFORMATION ABOUT TOBACCO CONSUMPTION

- **French study:**

Sources of smoking data, method of estimation:
Information about smoking was derived from the health archives of the COGEMA. Medical files exist but they contain generally no information about smoking and quality of information is relatively poor when available (no duration, no quantity…). So this source of information about smoking appears to be insufficient.
A second source of information was considered: questionnaires were created and a former miner interviewed either alive controls or relatives of cases and deceased controls. These interviews are still ongoing.

Proportion of missing data:
Medical files were found in high quantity (for 82% of cases and 83% of controls) but with poor information about smoking (for 36% of cases and 23% for controls).
The second phase of data collection is still ongoing. A first subset has been completed in the mining region of "Vendée". 92 questionnaires have been successfully completed, among a total of 115 miners residing in this area. Interviews have some disadvantages (contacts by phone and at home, age of people interviewed…) and necessitate a lot of time, but information collected is very complete and of very good quality (quantity, duration, year of beginning…); compliance appears also very good (only three refusals at the date of June 2003). 78% of cases and 81% of controls living in "Vendée" had smoking information (ongoing – at the date of June 2003).
In conclusion, this approach appears more promising than was the research from medical files. Nevertheless, the collection of data from questionnaires is still ongoing and the description of the data is too preliminary to be presented at this step.

- **Czech study:**

Sources of smoking data, method of estimation:
Information on smoking was collected differently in each sub-cohort. Smoking data in the N sub-cohort were collected routinely during regular medical checks. Smoking data among cases (N=265) in the S sub-cohort were extracted from medical files, whereas information among alive controls (N=241) were obtained from simple questionnaires sent by post or by personal interview. Information from deceased controls was obtained by means of the same questionnaires sent to the relatives of subjects. As it was not possible to obtain detailed smoking data from relatives, the questionnaire contained only basic information on ever/never smoking, year of cessation and number of cigarettes smoked daily. Missing individual data on number of cigarettes were replaced by respective means among cases and controls. In calculation of pack-years, it was assumed that all miners started smoking

at age 20. For controls, all temporal variables related to smoking (time since cessation, pack-years) were considered at the index year (year when the corresponding case died).

Proportion of missing data:
Among all 488 possible cases, information on smoking were obtained for 320 (66%) subjects. Smoking data among controls were collected only for those subjects who matched to the 320 cases, reducing the total possible controls to 960. Information on smoking was obtained for 689 (72%) of them.

- **German study (WP2):**

Sources of smoking data, method of estimation:
Information on smoking was derived from questionnaires sent to either alive controls or relatives of cases and deceased controls. Smoking information was collected from the Health Archive too, but was not available for analysis at the time of the project's end. At the time being, smoking information consist only on smoking status.

Proportion of missing data:
Questionnaires were available for 267 cases and 666 controls, which equals response rates of 37.8% and 47.2%, respectively. Among these available questionnaires, for 61 cases and 103 controls (i.e. 22.8% and 15.5%, respectively) there was no information on smoking. With respect to smoking, the proportion of missing data is 70.8% for cases and 60.1% for controls, if based on questionnaires.

- **German study (WP3):**

Sources of smoking data, method of estimation:
A lifelong smoking history was taken from all study participants. Subjects were defined as smokers if they had smoked regularly (at least one cigarette per day, 4 cigarillos/week, 3 cigars or 3 pipes/week) for at least six months at some time in life. Smoking exposure will be explored in a series of phases, where a new phase was defined as a change in amount or type of tobacco product smoked. In each phase information was available on the type of tobacco, amount smoked, duration in years, times of cessation, and year of starting. Smoking was included in all models by fitting pack-years as a continuous variable (log (pack-year+1)), consumption of other tobacco products as a binary variable, and time since quitting smoking in 4 categories. As expected, the proportion of smokers (89%, cases and controls combined) among miners was higher than in the general population.

Smoking status is described for cases and controls for the Czech and German (WP2 and WP3) studies in Figure WP2.4. The proportion of current smokers is higher for cases than for controls, while ex-smokers are in greater proportion among controls, except in the German (WP2) study.

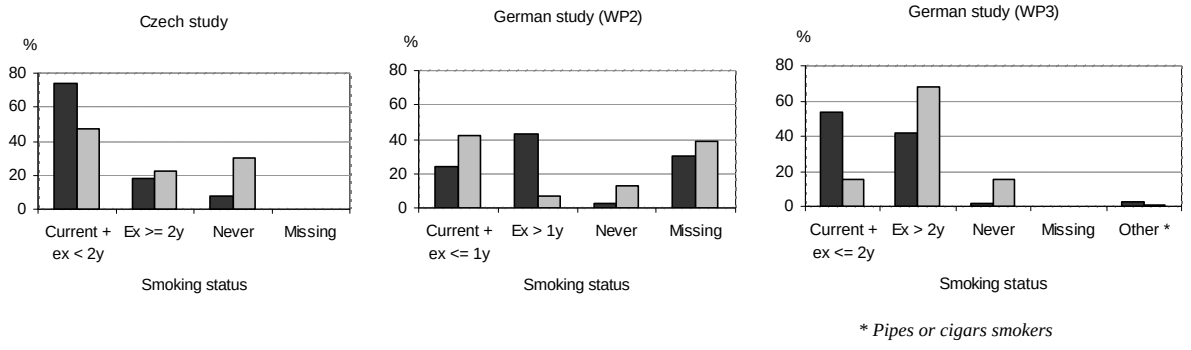

Fig. WP2.4: Smoking status for cases (dark bar) and controls (grey bar) for the Czech and German (WP2 and WP3) nested case-control studies

Description of quantitative data for the Czech and German (WP3) studies is given in tables WP2.5a to WP2.5b. The smoking exposure of controls was truncated at the date of death of case for the Czech study and at the date of lung cancer diagnosis of the respective case for the German study (WP3).

Table WP2.5a: Description of smoking exposure for the Czech nested case-control study, among current and ex smokers

	Cases (N=296)		Controls (N=484)	
	m	sd	m	sd
Age at beginning *	20		20	
Age stopped (index year)	55.3	10.2	52.0	10.7
Number of years smoked	35.3	10.2	32.0	10.7
Number of cigarettes per day **	22.5	10.8	20.8	10.5
Number of pack-years **	39.6	21.6	33.8	20.9

** not available – assumed 20*
*** missing individual information (N= 26 cases and 26 controls) replaced by means among cases and controls*

Table WP2.5b: Description of smoking exposure for German nested case-control study (WP3), among current and ex smokers

	Cases (N=486)		Controls (N=898)	
	m	sd	m	sd
Age at beginning	18.8	4.3	19.1	4.6
Age stopped (index year)	54.1[a]	11.6	43.6[b]	12.0
Number of years smoked	37.3	12.6	26.7	13.9
Number of cigarettes per day	14.6	6.1	11.9	6.5
Number of pack-years	28.1	15.4	17.1	13.4

a: N=282; b: N=747

4. ANALYSIS OF THE RISK OF LUNG CANCER DEATH ASSOCIATED WITH SMOKING AND RADON

- **French study:**

Conditional and unconditional logistic regression will be used to analyse the lung cancer risk associated with radon and smoking exposure. It is not possible to analyse effect of smoking exposure at the time being. Analysis of risk associated with radon only is coherent with results from the cohort analysis.

- **Czech study:**

Unconditional logistic regression is used to analyse the lung cancer risk associated with radon and smoking exposure. The adjustment variables are the year of birth, the attained age at index year and the sub-cohort.
Models of relative risk from radon and smoking used in the nested case-control study are:

$RR = 1 + b\ WLM$ (model 1)
$RR = r_S\ (1 + b\ WLM)$ (model 2)
$RR = r_S\ (1 + b_S\ WLM)$ (model 3)

Table WP2.7: Estimates of ERR/WLM (b) from the Czech nested case-control study

Model		ERR/WLM*	95%CI
1	smoking ignored	0.023	0.011 - 0.035
2	smoking adjusted	0.022	0.010 - 0.034
3	never smokers	0.047	-.000 - 0.270
	ever smokers	0.020	0.012 - 0.034

** ERR/WLM from exposure window 5-34*

Table WP2.8: Estimates of relative risk from smoking (r_S) in model 3 from the Czech nested case-control study

Smoking category	r_S	95%CI
never	1.0	
ex-smokers (quitted before 20y)	4.0	1.2 - 13.2
other smokers	10.6	3.4 - 33.2

Table WP2.9: Relative risk from radon and smoking from the Czech nested case-control study

Radon cumulative exposure	Never smokers	Ever smokers
not exposed	1	10.6
20 WLM	1.9	14.8
50 WLM	2.4	21.2
100 WLM	5.7	31.8
200 WLM	10.4	53.0

Results from the present nested study based on 320 cases and 689 controls are preliminary, as collection of smoking data is continuing. The difference between risk coefficients (ERR/WLM) when smoking is ignored and adjusted is negligible. But the relative risk from radon among non-smokers is higher by a factor of 2.3 in comparison to smokers, suggesting different patterns of lung deposition and clearance among smokers and non-smokers. The estimated interaction factor is not significantly different from one (95%CI: 0.5 – 10), but the magnitude of the interaction is similar to the value 2.1 estimated earlier from 6 studies of miners [BEIR VI 1999]. In all studies on smoking-radon interaction, the analyses substantially depend on numbers of non-smoking cases. In the present study, there were 24 such cases and in the BEIR VI analysis 64 cases. When several studies are combined, statistical power will increase.

- **German study (WP2) :**

Due to the fact that the exposure estimates are preliminary and the smoking information is not yet complete, i.e. data from the Health Archive are missing, no risk calculation can be done for the German nested case-control study (WP2). When all data are available, conditional logistic regression will be used to analyse the lung cancer risk associated with radon and smoking exposure.

- **German study (WP3) :**

For the time being, it is not possible to analyse the effect of radon exposure and smoking. Conditional logistic regression stratified according to year of birth has been used to analyse the effect of smoking exposure only on lung cancer. Table WP2.10 shows the increase of lung cancer risk according to cumulative amount smoked ignoring WLM. Smoking was associated with an odds ratio of 10.3 (95% CI: 5.2-20.4) compared to never-smokers. Lung cancer risk increased with cumulative amount smoked as shown in Table WP2.10. The smoking exposure of controls was truncated at the date of lung cancer diagnosis of the respective case.

Table WP2.10: Risk of lung cancer according to cumulative amount smoked in pack-years *

	Cases		Controls		Risk estimate with 95%-CI	
	N	%	N	%	Odds Ratio	
Never smokers	9	1.8	165	15.3	1	(reference)
0 - <20 pack-years	149	30.1	583	54.8	4.9	(2.4, 9.8)
20 - <40 pack-years	238	48.1	253	23.8	17.8	(8.9, 35.8)
40+ pack-years	99	20.0	62	5.8	31.0	(14.7, 65.4)

** excluding smokers of other tobacco products (pipes, cigars)*

The previous data, generated with a probably invalid JEM, showed no association between smoking and the level of radon cumulative exposure.

5. ADDITIONAL OBJECTIVES OF WP3

Silicosis

Most epidemiological studies show that the relationship between lung cancer and silicosis is even stronger than the relationship between lung cancer and silica exposure. This might reflect the fact that the fibrotic changes of the lung tissue in silicotics are in themselves a cancerous stimulus or that those who develop silicosis might have been higher exposed and therefore carry a greater lung cancer risk. X-rays of the lungs were taken of nearly all patients with lung cancer during their hospital stay and for most of the controls as part of their ongoing health program. Chest x-rays from former Wismut workers with lung cancer were collected in the study clinics. Two experts independently read the x-rays in order to classify the status of silicosis according to WHO-ILO criteria. The rating appeared to be problematic, since the classification scheme was developed for surveillance of healthy workers exposed to dust rather than of patients with lung cancer and silicosis as a second diagnosis. Very often it proved to be impossible to differentiate between findings like pronounced interstitial markings or angiomatosis carcinomatosa secondary to the tumour and the typical findings of silicosis. To find out what percentage of false positive diagnoses of silicosis we would have to expect under these conditions, a feasibility study was done. A total of 100 patients with lung cancer – 50 with former occupational exposure to silica and 50 without – were blindly classified according to ILO criteria on the tumour free side of the thorax. There was no false positive diagnosis of silicosis above stage 1/1.

The x-rays of 358 patients with lung cancer and of 469 controls, all of them former underground workers of the Wismut Company, were diagnosed according to the ILO-criteria of silicosis. Among the cases 51 had to be excluded, because they had a tumour on both sides of the lung, which made the classification impossible. In addition 11 patients and 17 controls were excluded due to serious technical shortcomings of their x-rays.

268 (90.5%) of the cases and 423 (93.6%) of the controls had no radiological signs (ILO 0/0 or 0/1) of silicosis. The results in detail are presented in Table WP3.1. As the estimation of exposure to silica dust is still under revision, the stage of silicosis cannot yet be correlated to silica exposure. Silicosis was less common than expected in our study population, probably because workers with silicosis developed the disease already at the time – or shortly afterwards – of very high exposure between 1950 and 1960. Premature death may have prevented participation of diseased workers in a case-control study that took place comparatively late between 1991 and 1999.

Table WP3.1: Radiological signs (ILO criteria) of silicosis in the German case-control study

ILO	Cases (n=296)		Controls (n=452)	
0/0	240	81,1%	396	87,6%
0/1	28		27	
1/0	13	14,5%	13	10,6%
1/1	2		8	
1/2	5		2	
2/1	2		2	
2/2	5		1	
2/3	1	4,4%	1	1,8%
3/2	0		2	
3/3	0		0	
3/+	0		0	

Indoor radon measurements

The mining regions of Thuringia and especially Saxony are well known for their relatively high exposure to radon in homes. Taking into account that quite a proportion of former miners was highly exposed underground only for a short period, but might has experienced a low-dose exposure at home over a very long period, indoor radon measurements were considered important for adjustment purposes.
In context to WP3, FIGH-CT-1999-000008 “Radon Epidemiology”, glass-based measurements were performed in a subset of 250 former Wismut employees (123 cases and 127 controls), who were willing to participate in the study and who had suitable glass objects in their homes. Interviews were performed, and detectors for glass and air measurements were placed. Meanwhile all detectors placed on the surface of glass objects have been collected and readings of these detectors will be available by the end of 2003.

6. DISCUSSION

Many cohort studies have been published on underground miners, especially on uranium miners [Lubin 1994, BEIR VI 1999]. Among those studies, only 6 have considered combined effect of tobacco and radon exposure on lung cancer: China, Colorado, Newfoundland, Sweden, New Mexico and Radium Hill cohort studies [Lubin 1994, BEIR VI 1999]. These studies have been limited for characterizing the joint effect of the two exposure factors by the extent of the data available on the smoking habits of the miners obtained through surveys or at the time of medical examinations (Table WP2.11).

A study based on non-smoking uranium miners [Gilliland 2000] had results consistent with an inverse exposure rate effect of radon, as in studies of non-smokers and smokers combined [Hornung 1998].

Our work in the frame of this project showed that the collection of data about smoking was not an easy task. The approach of estimation of joint effect of smoking and radon was limited by the availability of data (for example in the medical files in the French study) or by the percentage of response (the German questionnaires).
Our project provides a large dataset with both estimates of tobacco consumption and cumulative radon exposure. As a whole, if we sum the 4 studies, the number of miners is around 1000 cases and 2000 controls, with a large proportion with low levels of exposure to radon.

Table WP2.11: Summary of ascertainment and availability of tobacco use information

Study	Range of cumulative WLM	Number and percentage of cases with smoking information	Source of smoking data
China tin miners *	< 200 - ≥ 800	907 cases - 93% (77% of the cohort)	From 1976 lung cancer screening, ascertained at time of entry into cohort
Colorado Plateau uranium miners *	< 600 - ≥ 1600	292 cases - 80%	From medical examination between 1950-60 and a series of surveys between 1963-69 carried out at irregular intervals
Colorado Plateau uranium miners [Hornung 1998]	< 400 - ≥ 2000	224 cases - 59% (66% of the cohort)	New smoking data with survey conducted in 1986 + 8 y of follow-up
Newfoundland fluorspar miners *	< 400 - ≥ 1600	25 cases (48% of the cohort)	From surveys conducted in 1960, 1966, 1970 and 1978
Newfoundland fluorspar miners [Morrison 1998]	< 25 - ≥ 3500	90 cases - 65% (65% of the cohort)	+ 6 additional years of follow-up and from 1993 survey
Sweden iron miners *	< 50 - ≥ 150	51 cases	From 1972-73 survey of all active miners, 1977 survey of pensioners, and next-of-kin survey of deceased cases
New Mexico uranium miners *	< 200 - ≥ 400	52 cases (88% of the cohort)	At time of physical examination at Grants Clinic
Radium Hill uranium miners *		29 cases - 54%	From survey of all cohort members and next-of-kin, started in 1984
Ontario uranium miners [Finkelstein 1996]	< 15 - ≥ 80	42 cases (96% of the cohort)	From 1974 survey

** Source: Lubin 1994, BEIR VI 1999*

In the French study, smoking information was found from medical files for 43 and 26 % of selected cases and controls, respectively. At that time, the ongoing survey has given smoking information for around ten additive percent of them.
In the Czech study, there are 320 cases and 689 controls with smoking information and with cumulative exposure lower than 800 WLM, i.e. all the miners of the case-control study (selection criteria).
In the German study (WP2), there are 140 cases and 165 controls with smoking information and with cumulative exposure up to 1600 WLM, which represents 21 and 13 % of selected cases and controls, respectively.
In the German study (WP3), there are 495 cases and 1063 controls with smoking information (98 and 99 % of selected cases and controls, respectively). Cumulative radon exposure is not yet available for each individual.
For WP3 study, information collected on smoking habits is very complete: smoking status (smoker, ex-smoker or never smoker), duration (date of beginning and of ending), quantity (among current and ex-smokers) and type of tobacco (cigarettes, cigars, pipe). At that time, France and Germany (WP2) nested case-control studies had encountered many difficulties to collect available smoking data.

Previous analyses are consistent with a multiplicative relationship between radon-progeny exposure and current smoking and the risk of lung cancer [Morrison 1998, Yao 1994, Whittemore and McMillan 1983]. Furthermore some studies suggested the existence of a sub-multiplicative, greater than additive, interaction between radon and smoking [Hornung 1998, Yao 1994]. One isolated study found no significant interaction between radon and smoking [Finkelstein 1996]. In our project, preliminary results from the Czech study seems to confirm the existence of a sub-multiplicative interaction between radon and smoking exposure, even though interaction was not significant.

7. PERSPECTIVES

The perspectives are:

- to finish the completion of the data: collection of smoking data for the French study; correction of radon exposure assessment (JEM) in the German studies; and inclusion of recent cases and controls in the Czech study,
- to analyse the risk associated with both radon exposure and smoking in the four nested case-control studies,
- to evaluate the feasibility of a joint analysis of part of the data of the four studies, which will be based on a large dataset and will allow a higher statistical power.

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WORK-PACKAGE 4: ANIMAL DATA

Principal contractor: CEA, G Monchaux (now at IRSN)
Participants: CEA (J.P. Morlier), AEAT (C. Collier)

OBJECTIVES

Prior to the start of this contract (under EC 3rd and 4th Framework Programmes), in both France and UK, animal studies had been conducted to investigate lung tumour induction, following inhalation exposure by radon/radon daughters [Collier 1999, Cross and Monchaux 1999, Dano 2000, Monchaux 1999, Monchaux 2000, Monchaux and Morlier 2000, Monchaux 2001a-b, Morlier 1999a-b]. The later experiments were designed specifically to provide information on the dose ranges where inverse dose-rate effects are observed. The influence of co-factors such as diesel exhaust or tobacco smoke was also investigated, as were the effects of the degree of attachment of radon progeny and animal age at exposure. At the start of the current contract (EC 5th Framework Programme), the analysis of these studies was not fully completed and for the two partners (CEA partner 5 and AEA partner 6), the current contract had the specific objectives of completing the analysis and providing the data in a format suitable to the mechanistic modelers.

Mechanistic modelling applied to the animal data, along with that from the miners, aimed to provide a better description of the multistage carcinogenesis model implied after chronic alpha exposure, with or without cofactors. Provision of the animal data from both partners to the modellers in WP5 allowed experience from the 2-3 stage mutation model applied to relatively high exposed Colorado miners to be tested on the animal data and compared with that for the low level exposed European miners.

PROGRESS AND RESULTS

Under the EC 4th Framework Programme, a new series of experiments was carried out to investigate specifically the influence of exposure rate on lung cancer induction in rats. These studies were conducted at relatively low cumulative exposure comparable to lifetime exposures in high-radon houses or current underground mining exposures of around 100 WLM (0.36 J h m^{-3}).

The animal experiments were conducted concomitantly at CEA (France) and AEA-Technology, plc (Harwell, UK). Where possible, the experimental conditions used at the two laboratories were similar, for example both groups used rats of the same strain, sex and age. In addition, the metrology of the radon exposure atmospheres and the reporting of pathology were standardised between the two groups. The principal differences between the exposure conditions were that exposures were conducted during the working day at CEA, without introduction of carrier aerosol, whereas they were conducted continuously at Harwell (24 hours per day), using Carnauba wax as a carrier aerosol.

1. RADON EXPOSURE - CEA PARTNER 5

Exposures to radon and its progeny were designed to investigate the role of potential alpha energy concentration (PAEC) and protraction of exposure that have been shown to be the most important parameters for lung cancer induction in experimental animals. All the animal exposures were performed at the CEA-University of Limoges radon inhalation facility, located in Razès (France), on the site of the former French uranium mines. Radon gas emanation from uranium ore was introduced

into the 10 m^3 stainless steel chambers through a dilution system and the radon progeny were attached to the ambient aerosol (natural aerosol) [Monchaux 1994, Monchaux 2002a-b]. The duration of exposure sessions was 6 hours. Exposures were conducted under static conditions without air renewal in the chambers. During the exposures, monitoring of the PAEC, equilibrium factor F, unattached fraction f_p, radon progeny concentrations and environmental conditions were performed using recognised methods agreed between AEA and CEA in previous metrology inter-comparison exercises [Strong 1996].

2. ANIMALS AND HISTOLOGICAL ANALYSIS - CEA PARTNER 5

After exposure, rats were kept and regularly observed until death and killed when moribund. At necropsy, a complete examination of all the organs was performed and any abnormalities were recorded. The lungs were carefully observed and any nodules detected by a gentle palpation. Lungs, selected organs and organs with suspicious lesions were taken systematically for histo-pathological examination. Lungs were fixed *in situ* by intra-tracheal instillation of 10% neutral buffered formalin (NBF). Thoracic lymph nodes and surrounding tissues from the mediastinal region, including heart, were fixed all together. If no lesion was observed, samples from liver, spleen, kidneys and the whole brain were fixed in NBF after all the organs had been systematically weighted. Any suspicious lesion from other organs was taken and fixed. Sagittal sections of the nasal and para-nasal cavities were performed and any macroscopic lesion fixed. Tissues were fixed in NBF by immersion before processing and embedding in paraffin wax. Serial 5-µm thick sections were performed taking care to trim only the sufficient tissue for histo-pathological diagnosis in order to keep remaining tissue from the lesion available for further studies on biological markers. Routine process consisted in haematoxylin-eosin-saffron staining. In addition, selected special staining including Alcian-blue for mucus detection in adenocarcinoma and/or immuno-histochemical methods was used. Proliferative preneoplastic lesions and lung tumours were classified according to the classification published in the EULEP Color Atlas [Hahn and Boorman 1997].
Lung carcinomas were differentiated into adenocarcinomas, squamous cell carcinomas and adenosquamous carcinomas. Adenocarcinomas could develop from any level of the respiratory tract and consisted of papillary neoplasms with well-differentiated cuboidal or columnar cells. They could be subdivided into mucus secreting (formerly classified as bronchogenic carcinoma), non-mucus secreting (formerly classified as non-bronchogenic carcinoma), anaplastic (undifferentiated) or large cell (poorly differentiated) types. Bronchiolo-alveolar carcinomas consisted of non-secreting papillary patterns of cuboidal cells from alveolar origin (type II alveolar cells) with dark round-shaped nuclei of different size. They frequently invaded the mediastinum. A more alveolar type without papillary features was also observed. Rat bronchiolo-alveolar carcinomas were mainly classified as adenocarcinomas. Squamous cell (epidermoid) carcinomas consisted of irregular proliferation of stratified squamous epithelium that could be well or poorly differentiated. Adenosquamous carcinomas contained both glandular and squamous tissue. Lung carcinomas were scored using a classification derived from the tumour-node-metastasis classification [Renaud and Merlier 1975].
Preneoplastic lesions and pulmonary benign lesions were differentiated between non neoplastic proliferative lesions, including - alveolar epithelial hyperplasias and squamous cell metaplasias -, and pulmonary benign tumours, adenomas. Survival times and age at death of each rat were also recorded.

The highest global incidence of lung cancers and the highest proportion of squamous cell carcinomas, were observed in rats exposed at high PAEC. In the other groups of rats, the global incidence of lung cancers and the relative frequency of squamous cell carcinomas decreased with decreasing PAEC, i.e., decreasing exposure-rates. The larger and most invasive tumours were also observed in rats exposed at high PAEC and the size and invasiveness of tumours decreased with decreasing PAEC and/or protraction of exposure. Similarly, the number of non-neoplastic proliferative lesions and pulmonary benign tumours, in particular, the proportion of alveolar epithelial hyperplasia and adenomas decreased with decreasing PAEC.

A full analysis of the data was completed by the end of the year 2001 and the results were published (see list of publications).

3. RADON EXPOSURE - AEA PARTNER 6

In the period 1994-1998, more than 2000 adult male rats (Sprague Dawley, Charles River UK) were exposed to radon/radon progeny at AEA Technology Plc in a purpose built facility [Strong 1996]. For each exposure, approximately 40 rats were held in cages in each exposure chamber, two per cage. Animals for the carcinogenicity studies were exposed continuously for periods of between 24 and 150 hours. Where exposures of longer than 150 hrs were required, exposures would cease for a period of approximately 24 hrs to allow cleaning of the chamber and then resume. The longest exposure took 142 days to complete. During all exposures radon progeny concentrations (^{218}Po, ^{218}Pb and ^{214}Bi) in the chamber were measured hourly using a semi-continuous measuring system which also provided information on the "unattached" fraction of these nuclides. Carnauba wax aerosols were generated using an evaporation and condensation technique similar to that described by Tu [1981] and had a count median diameter of 0.15 µm measured with a differential mobility particle sizer (Model 3932, TSI Inc., Minnesota). Aerosol concentrations in the chamber were of the order 8 x 10^4 cc^{-1} and provided an atmosphere with a potential alpha energy "unattached" fraction of less than 1.5%. From each exposure sample animals (usually 2) were killed for the deposition measurements. These were normally exposed for a minimum of four hours and then removed from the chamber. They were killed by interperitoneal injection of sodium pentabarbitone. The lungs were excised, weighed and then the radon progeny concentration was determined by gamma spectrometery. Deposition of radon progeny was found to be proportional to PAEC and exposure duration [Strong and Baker 1996].

The exposures were conducted in 3 studies to investigate the effect of dose, dose rate and dose rate at low cumulative doses. To determine the tumour incidences in these animals, each animal was allowed to live its life span. At the start of this contract, 72 animals remained alive. The specific objectives for this partner were:

- The maintenance of these animals in keeping with the previous conduct of the study and the completion of the life-span studies,
- The processing of tissues taken from animals on life-span study through paraffin wax through to Haematoxylin and Eosin stained slides
- The reading of the pathology of the prepared slides from the life-span study

4. ANIMALS AND HISTOLOGICAL ANALYSIS - AEA PARTNER 6

Animals were maintained under the conditions required by the Animals (Scientific Procedures) Act 1986. Each animal was examined weekly and any findings recorded. When the animal either became moribund and was killed or died, a necropsy performed immediately. Some animals died before they showed any clinical signs. Animals were checked every day and necropsies were performed on any animals that had died. Lung tissue from all animals and any tissues showing abnormalities at necropsy were fixed for preparation of histological slides.
By June 2000 all remaining AEA animals had reached the end of the life span analysis. At the start of the contract histopathological analysis was complete on nearly 500 animals. Analysis involved preparation of slides by histology according to methods in agreement with those of Partner 5 and reading of the slides by a qualified pathologist. Analysis of all animals was completed in April 2002.

5. ANALYSIS OF DATA FROM BOTH PARTNERS

Following the finalisation of the histopathological analysis for each animal, both partners constructed a database for each study. This gave for each animal:

- details of duration and level of exposure attained (concentration and cumulative exposure);
- duration of lifespan and nature of death (i.e. whether the animals was killed in extremis or died);
- diagnoses of malignant and benign lung tumours classified according to a procedure agreed between the partners;
- diagnosis of other diseases including benign and malignant tumours which resulted in clinical observations outside of the lung.
- For lung tumours an assessment of whether or not the tumour was expected to be fatal or not based on a calculation of fatality index which took into account the size of the tumour, whether it had invaded the pleura, whether there were metastases. These assessment criteria have been found to be comparable with a similar index used for Batelle rodent and dog data.

A tumour was considered as fatal if one of the following criteria was satisfied [Dagle 1993]:

presence of a single metastasis or multiple metastases,
tumour size depending on the structure affected, but generally < 15 mm diameter,
presence of marked necrosis affecting more than 50 % of the lesion,
extensive invasion into pleura, bronchi and/or blood vessels.

For the classification of fatal tumours it can be summarised as in Table WP4.1. In this table the groups of animals exposed in each experiment are identified by group name, the cumulative exposure (WLM) gives the total exposure, the exposure concentration gives the average concentration of radon/radon progeny in the chamber during the exposures. The exposure rate is the cumulative exposure (WLM) divided by the number of days the exposure took place over. The incidence of fatal lung tumours is the number of animals showing fatal lung tumours as classified by the system defined above.

Relative and absolute risks have been calculated and data for both partners are plotted in figures WP4.1-4 against exposure concentration and cumulative exposure. Figures WP4.1 and WP4.3 show that the risk of fatal lung tumours increases with cumulative exposure. This increase is observed already at low levels of exposure, i.e. below 500 WLM. Figures WP4.2 and WP4.4 show that the risk of fatal lung tumours also increases with exposure rate.

Table WP4.1: Incidence of fatal lung tumours in rats exposed to radon and radon progeny in CEA and AEA studies.

Exposure group	Cumulative exposure WLM	Exposure concentration WL	Exposure rate WLM/day	Exposure duration days	Number of fatal lung cancers	Number of rats at risk	Incidence %	Relative risk %	Excess absolute risk %
CEA Rn25LDR	25	2	0.05	500	1	497	0.20	3.06	0.14
CEA Rn25HDR	25	100	0.25	100	2	496	0.40	6.14	0.34
CEA RnD6	42	18	0.24	175	2	211	0.95	14.43	0.88
CEA Rn50HDR	50	100	0.25	200	13	497	2.62	39.81	2.55
CEA RnD1	105	188	3.50	30	14	240	5.83	88.78	5.77
CEA RnPr	107	147	1.30	83	4	240	1.67	25.37	1.60
CEA RnD3	100	58	1.10	90	5	240	2.08	31.71	2.02
CEA RnD12	100	13	0.26	375	8	240	3.33	50.73	3.27
CEA Rn200	200	1200	5.00	40	8	199	4.02	61.19	3.95
CEA Rn500	500	1200	10.00	50	15	99	15.15	230.61	15.09
CEA Rn1,000	1000	1200	20.00	50	15	100	15.00	228.30	14.93
CEA Rn3,000	3000	1200	3.30	90	10	50	20.00	304.40	19.93
CEA Rn6,000	6000	1200	3.30	180	2	50	4.00	60.88	3.93
AEA DR 1	184	1308	184	1	0	101	0.00	0.00	-0.07
AEA DR 2	170	1340	12	14	4	52	7.69	117.08	7.63
AEA DR 3	387	1116	155	2-3	1	104	0.96	14.63	0.90
AEA DR 4	785	1000	69	4-20	0	102	0.00	0.00	-0.07
AEA DR 5	1586	1158	108	13-17	4	102	3.92	59.69	3.86
AEA DR 6	3095	1029	69	45	2	44	4.55	69.18	4.48
AEA DRHD 1	1001	258	26	39	3	45	6.67	101.47	6.60
AEA DRHD 2	999	511	50	20	1	45	2.22	33.82	2.16
AEA DRHD 3	1007	1025	144	7	3	46	6.52	99.26	6.46
AEA DRHD 4	994	1880	249	4	5	52	9.62	146.35	9.55
AEA DRLD 1	99	15	0.7	139-142	3	190	1.58	24.03	1.51
AEA DRLD 2	101	178	0.9	94-116	1	186	0.54	8.18	0.47
AEA DRLD 3	108	882	1.2	88-89	1	183	0.55	8.32	0.48
AEA DRLD 4	99	158	0.9	115-116	1	184	0.54	8.27	0.48
Controls	0				1	1521	0.07		

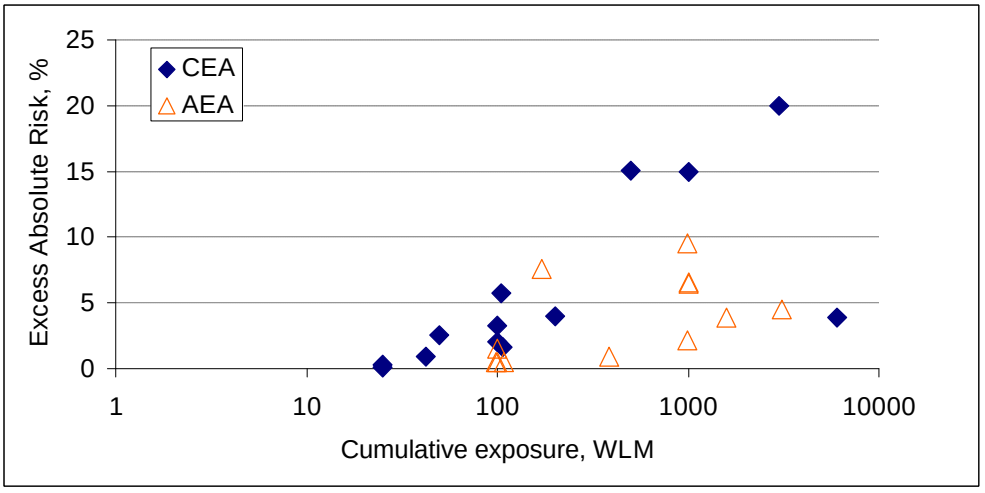

Fig. WP4.1: Lifetime excess absolute risk of fatal lung tumour in function of radon cumulative exposure (WLM, log transformed) in CEA and AEA studies

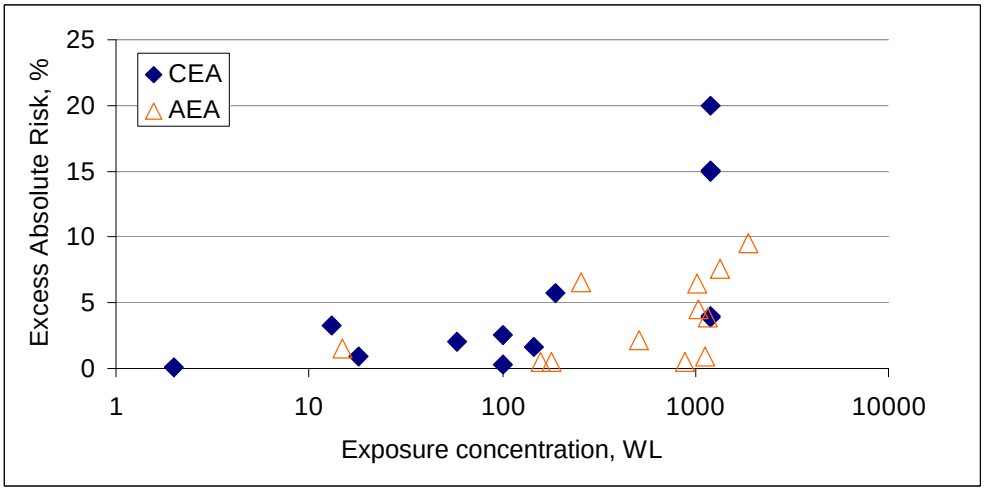

Fig. WP4.2: Lifetime excess absolute risk of fatal lung tumour in function of radon concentration (WL, log transformed) in CEA and AEA studies

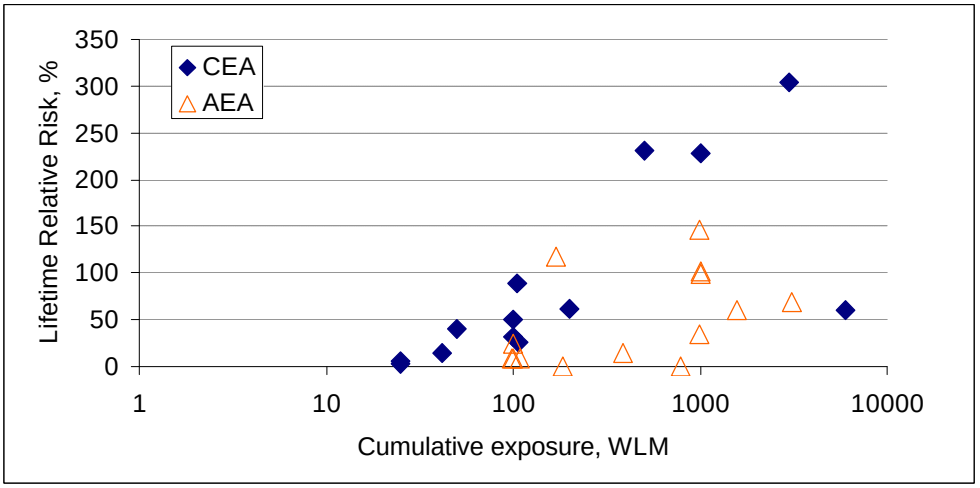

Fig. WP4.3: Lifetime relative risk of fatal lung tumour in function of radon cumulative exposure (WLM, log transformed) in CEA and AEA studies

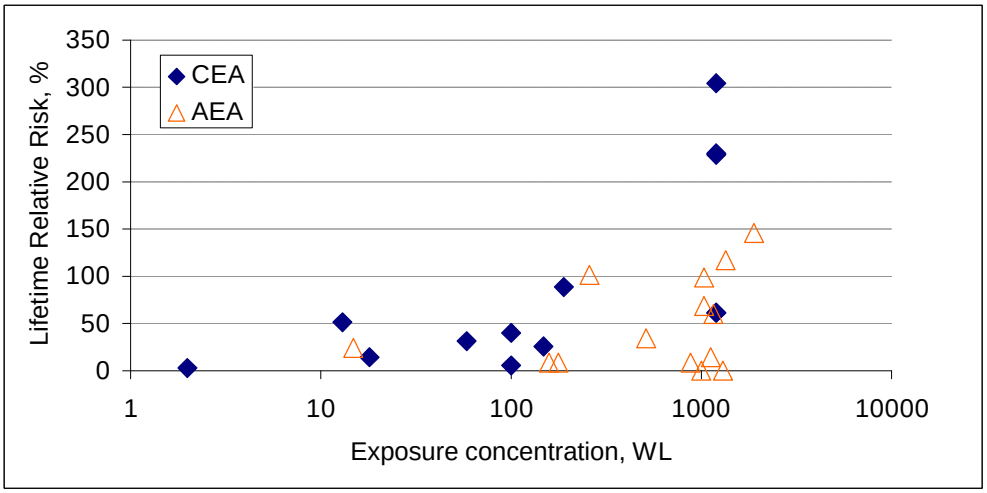

Fig. WP4.4: Lifetime relative risk of fatal lung tumour in function of radon concentration (WL, log transformed) in CEA and AEA studies

MAIN ACHIEVEMENTS

The main achievements of this work package have been the completion of animal studies and their histological analysis by both partners and the translation of the results into comparable databases. These databases have then been made available to the mathematical modellers of WP5 within this contract for modelling of lung tumour induction by radon progeny exposure in animals and comparison of the induction occurring in miners exposed at high and low levels. The databases and raw data will be transmitted to the European Radiobiology Archive and made available to other researchers interested in using the data.

DISCUSSION

It has been shown that at high cumulative exposures, the risk of lung cancers in rats increased with decreasing PAEC [Chameaud 1984]. This effect, which has also been observed in underground miners, is called the inverse dose-rate effect or protraction enhancement effect [BEIR VI 1999]. In contrast, the present results indicate that at relatively low cumulative exposures of about 100 WLM, comparable to lifetime exposures in high-radon houses or current underground mining exposures, the risk of lung cancer in rats decreases with decreasing PAEC, i.e., exposure-rate, confirming the results obtained at lower cumulative exposure [Morlier 1994].

Different analyses of various animal data sets have already been performed and the importance of categorisation of lung tumours as fatal or incidental to the death of the animals was discussed, recognised and a common strategy agreed. An analysis of fatal and incidental lung tumours was performed in rats from both AEA-Technology and CEA for which sufficiently detailed information was available. A full analysis of fatal tumours has been performed. These data were also taken into account in statistical modelling (WP5).

Roughly, it appears that the parameters that influence fatal lung cancer risk are cumulative exposure, PAEC, exposure-rate, time since exposure and protraction of exposure. The highest fatal lung cancer risk occurred in rats exposed at 100 WLM, at high PAEC (~ 200 WL), high exposure-rate (3.5 to 5 WLM/day), delivered for a short period (30 days). At low cumulative exposures (~ 50 WLM), the risk decreases with decreasing PAEC, decreasing exposure rates and increased protraction of exposure. At high cumulative exposures (= 200 WLM), the highest risk occurred in rats exposed at 500 WLM, high PAEC (1200 WL), high exposure-rate (10 WLM/day) delivered for a short period of time of about 50 days. At very high cumulative exposures (= 500 WLM), the risk decreases with increasing cumulative exposure, decreasing exposure rates and increasing protraction of exposure. The inverse exposure-rate effect was observed mainly at the highest exposure-rates.

Figure WP4.5 shows the combined influence of cumulative exposure expressed in terms of WLM and of PAEC, expressed in terms of WL, on the excess absolute risk per unit exposure (EAR per WLM) in CEA rats. For cumulative exposures higher than 100 WLM, and PAEC higher than 150 WL, the risk of fatal lung cancer decreases with increasing cumulative exposure and increasing PAEC. In contrast, for cumulative exposures lower than 100 WLM, the risk of lung cancer decreases with decreasing PAEC. Moreover, the risk of lung tumour induction in rats appears to be maximal for cumulative exposures ranging from 50 WLM up to 107 WLM, and PAEC ranging from 50 WL up to 188 WL.

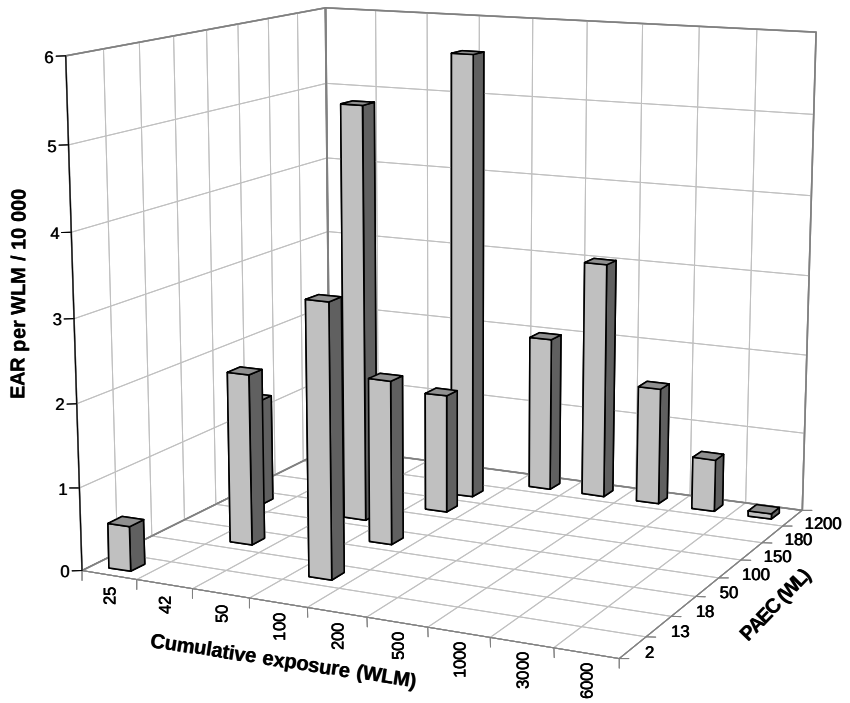

Fig. WP4.5: Schematic representation of lifetime excess absolute risk (EAR) per WLM of fatal lung cancer in CEA rats exposed to radon and radon progeny at various cumulative exposures (WLM) and exposure rates (WL).
PAEC: potential alpha energy concentration. Nota : x (WLM) and y axes (WL) are categorical.

These data suggest that the induction of lung cancer is the result of a complex interplay between cumulative exposure and exposure-rate, with an optimal combination of these two parameters. They support the hypothesis that, at low doses, the risk of lung cancer is governed by the rate at which the dose is delivered, and not by the total cumulative dose alone.

These data are also consistent with that from underground uranium miners showing an inverse dose-rate effect at high cumulative exposures, but a diminution of this effect at cumulative exposures lower than 50 WLM [Lubin 1994, Lubin 1995]. These data support both an inverse dose-rate effect at high cumulative exposures, as well as its diminution or disappearance at low cumulative exposures.

Quantitative modelling of data from animal studies provided risk coefficients that can be compared with similarly derived coefficients from epidemiological data. Different applications of two-step mutation models were tested in two largest data sets of rats exposed from both PNNL in USA and CEA-COGEMA in France, as well in various miner studies [Gilbert 1996, Heidenreich 1999]. During this contract, a risk analysis of animal data was performed in connection with partners from WP5. This allowed comparison of the different data sets of recent animal data from partners 5 and 6 on exposure rate with those of previously analysed data, to scale biological parameters and risk between rats and humans and to achieve statistical modelling of the underlying mechanisms.

A joint analysis of both AEA-Technology and CEA data is in preparation for publication.

PUBLICATIONS AND SCIENTIFIC COMMUNICATIONS

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WORK-PACKAGE 5: MECHANISTIC MODELLING OF LUNG TUMOUR DEVELOPMENT AFTER RADON EXPOSURE BASED ON HUMAN AND ANIMAL DATA

Principal contractor: NRPB, C. Muirhead
Participants: GSF (W. Heidenreich, C. Kaiser), NRPB (R. Haylock),
RIVM (M. Brugmans, H. Bijwaard, S. Rispens, H. Leenhouts)

OBJECTIVES

This work package had four main objectives. The first and over-riding objective was to investigate whether the two-stage mechanistic model of carcinogenesis could be used to model the effects of radon (and smoking) on lung cancer incidence and mortality using both historical and new animal datasets and epidemiological cohorts comprising of various new and old uranium miner datasets.

Secondly, it was intended to compare the model descriptions for the sets of rat data and the sets of human miner data to determine the level of agreement as to the effect of radon (and smoking) on the health risks.

Thirdly, it was desirable to find out if any of the datasets could be combined and fitted using a single model. Thus the ability with which the various datasets could be grouped together and fitted using a single model was of interest.

Finally, an investigation into the possibility of using case-control subsets of the miner data in place of the full cohorts was undertaken. It would determine if the use of case-control subsets instead of using the full cohorts would be possible.

1. INTRODUCTION

1.1 The two-stage carcinogenesis model with clonal expansion

The two-stage clonal expansion (TSCE) or two-mutation carcinogenesis (TMC) model aims to represent in a mathematical model the mechanism by which normal cells can be converted to malignant cells. A pictorial representation of the model is shown in Figure WP5.1. In the model the carcinogenic process is postulated to be the result of two events, namely the changing of a normal cell to an intermediate cell and the subsequent change of the intermediate cell to a malignant cell. After a lag-time (t_{lag}) a malignant cell will develop into a tumour. The two cell change events, normal to intermediate and intermediate to malignant, are broadly viewed as mutations occurring at some baseline rates which can be altered by exposure to radon and smoking. The model represents these cell change events as Poisson processes with stochastic 'mutation' rates μ_1 and μ_2. In the intermediate phase, the cells have a proliferative advantage that is modelled with stochastic birth and death rates (a and ß, respectively), the clonal expansion process. To allow for the growth time of a malignant cell into a clinical detectable tumour (in incidence data) or into tumour-induced death (for mortality data), a deterministic lag time is used. Fits to individual cancer data (for rats and miners) are made using a maximum likelihood technique that involves global and local search routines.

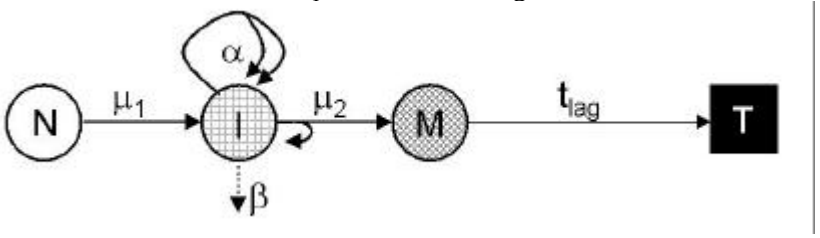

Fig. WP5.1: Schematic illustration of the two-mutation clonal expansion model.
N: normal cell; I: intermediate cell; M: malignant cell; t_{lag}: lag-time; T: tumour.

Each of the three partners working on WP5 has used slight variations of this model. RIVM does not allow the net growth rate of intermediate cells to depend on radiation dose, because there are no indications from cellular radiobiology that such a mechanism exists. In the version of the model used by RIVM, the net clonal expansion is modelled by a single parameter by setting ß=0 (see Brugmans 2002, for the motivation). The parameters that cannot be determined by a fit to cancer incidence data are pre-defined. These are the number of lung cells at risk, $N = 5\times10^5$ for rats and $N = 10^7$ for humans also the background mutation rates for both steps are assumed equal: $\mu_{1,bg}=\mu_{2,bg}=\mu_{bg}$. For the rat data, the lag time t_{lag} is fitted, while for the miner data a fixed period of 5 years is used. The effect of radon is incorporated by assuming dose-response relationships for the mutation rates that correspond with the relationships found in cellular radiobiology [Leenhouts and Chadwick 1994], i.e. a linear increase with exposure rate at low levels, in combination with an exponential decrease due to cell killing at high exposure rates. Thus the following expression for the dose-dependent parameters in the model is used:

$$m_i(D) = m_{bg} \cdot (1 + a_i D) \cdot \exp(-p_i D) \qquad \textit{Eq WP5.1}$$

where i=1,2 refers to the first or second mutation rate, a_i is the linear mutation induction coefficient, p_i is the cell killing coefficient and D is the dose per cell cycle. For the exposure to radon, the exposure rate (WLM/day) is used as unit for the dose per cell cycle.

At very advanced ages, baseline human cancer incidence data are known to decrease with age. Several mechanisms are likely to contribute to this feature. For lung cancer incidence data that are not stratified by smoking behaviour (like the French and Czech miner cohort data used here), part of the decrease may be caused by the longer survival of non-smokers vs. smokers. The decreasing incidence cannot be captured by the two-stage models as usually applied, thus an additional process in the model description is needed. To improve the description of the baseline cancer incidence of the full time-span, RIVM has introduced a mechanism in the model that makes the baseline incidence level and decrease at very advanced ages [Brugmans 2002]. This is done by slowing down the cellular activity at very high ages, that decreases all rates for the modelled processes. The optimal cellular activity function, that is unity at young ages and decreases with slope -0.042 y^{-1} around half-value age 76.3 y, was determined from the French and Czech miner cohort data and has been used as a fixed function in the fits of the radon effect. It should be noted that this 'slowing function' is used as an effective function that accounts for all processes that affect the cancer incidence at very advanced ages in an aggregate fashion.

In the version of the TSCE model used by GSF, the parameters that cannot be determined from experimental data alone are treated slightly differently. In the absence of radiation acting on the cell processes the GSF version of the model possesses five biological parameters N, m_1, a, b and m_2 of which only three are identifiable. These can be combinations of the form $Y_0 = Nm_{10}m_{20}$, $g_0 = a_0 - b_0 - m_{20}$ and $q_0 = \frac{1}{2}\left(-\gamma_0 + \sqrt{\gamma_0^2 + 4\alpha_0\mu_{20}}\right)$.

At young ages the number of intermediate cells is controlled by initiation. Hence, the hazard increases linearly with slope Y_0. Thereafter additional growth of intermediate cells comes from the positive net rate of clonal expansion. During this period the hazard shows an exponential gain governed by the time constant g_0. At old age a premalignant clone may die out if the death rate b_0 is larger than zero. Once a cell becomes malignant the sequence of carcinogenesis is terminated and further malignant cells do not affect the cancer risk. For these two reasons the hazard assumes a constant level of Y_0/ q_0. The lag time t_{lag} can be identified in principle since it affects a time shift to the right of the hazard function. Practically it is difficult to determine from spontaneous incidence data where there are not enough cases in early age.

The preferred model of GSF for the analysis of rat data was the so-called GSF-IP model where the cell mutation process of initiation and the clonal expansion depend on the irradiation dose d as follows:

$$Y(d) = Y_0\left[1 + Y_1 d \exp\left(-Y_2 d\right)\right] \qquad \text{for initiation}$$

$$g(d) = g_0 + g_2\left[1 - \exp\left(-\frac{g_1}{g_2}\right)d\right] \qquad \text{for promotion.}$$

1.2 The datasets

The analyses in WP5 are based on both animal (rat) experimental data and human epidemiological data. There are two categories of rat data. The historical data consists of two datasets, one collected at the Pacific Northwest National Laboratory (PNNL), USA, and one collected at the Commissariat à l'Energie Atomique (CEA) France. Of the two new rat datasets, one was also collected at CEA while the other is from AEA Technology PLC, Biosciences (AEAT).

The human data also fall into the same two categories of historical and new. The historical information comprised of a set of data from the Colorado Plateau uranium miners and one from tin miners from the Yunnan province of China. The new datasets are based on Czech uranium miners and French uranium miners (see WP1).

2. RESULTS

2.1 Application of the mechanistic model to animal data

2.1.1 Analysis of historic rat data

RIVM: Based on rat data available at the start of the contract, a joint analysis of PNNL and CEA rats with the TMC model was performed. In this analysis, the dose-response relationships for the model parameters were used that are described above (Eq WP5.1), i.e. mutation rates which are linearly dependent on exposure with an exponential decrease at high exposure rates and a dose-independent clonal expansion of intermediate cells. Maximum likelihood fits were performed assuming 'incidental' tumours in both data sets since in both data sets the time at which the first malignant cell developed cannot be determined from the tumour detection time. Separate fits of both data sets yielded very similar fitted parameter values, which showed that the close-to-linear dose response for the first mutation is one order of magnitude larger than the linear dose dependence for the second mutation, and that at higher dose rates the second mutation rate vanishes due to reduced survival of the mutations (cell killing). Notwithstanding the differences in the two experiments, a joint model fit described both data sets simultaneously without loss of statistical significance. Thus a consistent biologically based model solution for the development of lung tumours in radon-exposed rats was found for two large experimental data sets. This analysis was published in a scientific paper [Bijwaard 2001].

GSF : The TSCE model of cancer induction has been tested on recorded and simulated cohort data for radon-exposed rats. Unfortunately, different versions of the model, for which radiation acts on different biological processes, can each provide a good description of the data. This is the case for an initiation-transformation (IT) and an initiation-promotion (IP) model when they are applied to lung tumour data of radon-exposed rats and all malignant tumours are assumed to be incidental. However, if one were able to use information on fatal tumours as well, these two models can be distinguished by their deviances. This work has been published as a scientific paper [Kaiser and Heidenreich 2002].

The ability of ionising radiation to induce cancer in an irradiated organ is proven beyond doubt for medium and high doses. For radiation effects on non-cancer deaths there are conflicting claims. One approach to investigate possible non-cancer effects of radiation exposure is to study the longevity of exposed persons or animals compared to non-exposed ones. This analysis uses a large data set from rats exposed to radon and radon-progeny for that purpose. The emphasis of this analysis is on survival

for all endpoints of death, except fatal lung cancer. For the groups exposed to a radon concentration of 10, and 100 WL, the 50% survival for "all deaths competing with fatal lung cancer" is roughly constant up to the very high exposure of 5000 WLM, while for those with 1000 WL it is also constant, but significantly lower. The data suggest that the deaths from other causes than fatal lung cancers depend mainly on the exposure rate, rather than the exposure, up to very high exposures. This work indicates that looking at lung cancer only as an end point may provide too limited a view; the experimental data indicate that radon has other effects that modify the life-span, at least in animals. The analyses carried out in this work have been submitted for publication [Heidenreich et al., Submitted to *Radiation Research*].

Other analyses were carried out using data on rats exposed to cigarette smoke before or after exposure to radon. The object was to obtain estimates of the smoke-dependent parameters of the TSCE model. The data show a strong asymmetry: when the smoking exposure follows radon exposure, the number of lung cancer cases is massively increased, while in the reverse order, the effect of smoking is small. The spontaneous parameters and the action of radon acting on initiation and promotion are fixed, based on earlier work. Cigarette smoke acting on transformation, and inducing a reduction of the radon dose to the target cells after a smoking period gives an acceptable description of the data. A manuscript detailing this work has been submitted to a scientific journal.

2.1.2 Analysis of new rat data

RIVM: During the contract period, new CEA and AEAT rat data were provided by WP4. At the same time the original CEA data set was revised: a reduced group of historic controls was identified and a few extra, previously exposed groups were added. Several new fits were made with the TMC model to all data groups separately and jointly. In all fits the tumours were assumed 'incidental' since the time at which the first malignant cell developed could not be determined from the tumour detection time. It turned out that even though there was statistically significant justification to model some groups separately, a joint fit of all the rat data (more than 12 000 rats) represents all groups well. This joint fit resembles the published fit of old CEA and PNNL data and is presented in the graphs and tables below. These graphs and tables are prepared in a manner very similar to what was published in an intercomparison paper in which old CEA data were modelled [Heidenreich 2000]. This is done for ease of comparison. In the graphs and tables two model solutions are given: the preferred RIVM fit of all rat data (some 12 000 rats) and the GSF initiation-promotion fit (GSF-IP) for the GSF data selection (nearly 10 000 rats).

The dose rate dependency of the mutation and expansion rates is shown in figure WP5.2. The mutation rates are expressed relative to the background mutation rate which for the RIVM fit is set to be equal in both mutational steps and amounts to 1.21×10^{-6} w^{-1}. For the RIVM fit the first mutation rate appears to be sub linear and is more than two orders of magnitude larger than the second mutation rate (the linear coefficients differ by one order of magnitude) which exhibits strong cell killing at higher dose rates. The net growth rate is assumed dose-independent.

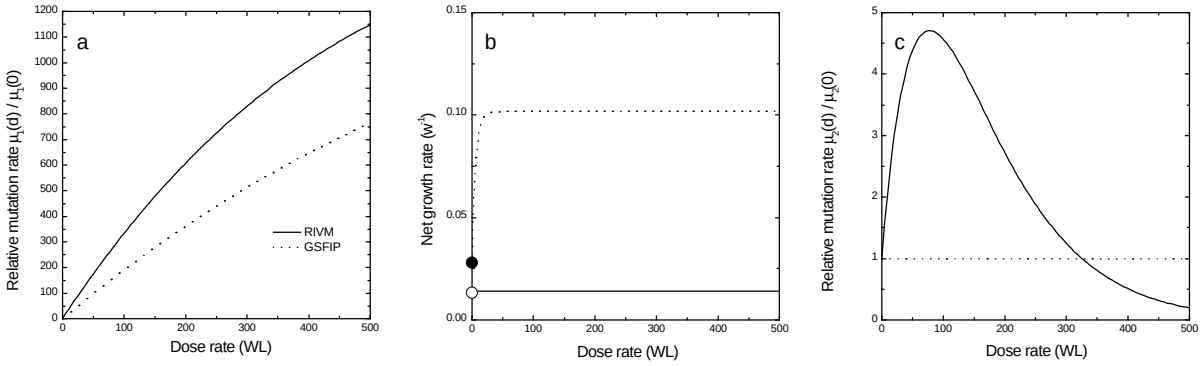

Fig. WP5.2: The (relative) mutation and expansion rates in the RIVM and GSF-IP model fits.

Table WP5.1: Some identifiable parameters for the GSF-IP and RIVM models of the rat data. The GSF-IP parameters have Wald-based standard errors.

Model	Number of free parameters	N $\mu_1(0)\mu_2(0)$ (10^{-6} w^{-2})	$\alpha(0)$-$\beta(0)$-$\mu_2(0)$ (10^{-2} w^{-1})	t_{lag} (w)
GSFIP	8	0.55±0.27	2.78±0.82	17.5±4.2
RIVM	7	0.73	1.40	18.4

A further specification of the preferred RIVM and GSF-IP models is given in table WP5.1. This table gives some identifiable parameters that can be compared to the intercomparison paper [Heidenreich 2000]. Note, however, that GSF and RIVM use different data selections.

In table WP5.2 the new rat data groups from CEA and AEAT are summarised and the RIVM and GSF-IP model fits to these groups are given in terms of the number of cases predicted and the number of cases observed. Note that the predicted values were taken from the joint fit in which, besides these new data provided by WP4, RIVM has simultaneously fitted 51 CEA and 31 PNNL groups, containing 4787 and 3880 rats, respectively. GSF also fitted much more data than given in the table.

Table WP5.2: New CEA and AEAT data provided by WP4 in groups delineated by different total exposure, exposure rate and/or begin time of exposure (for CEA data different exposure rates were used in the modeling by GSF and RIVM, indicated as GSF/RIVM). The last three columns give predicted number of cases according to the GSF-IP and the RIVM fit (both including old CEA and PNNL data, but using different data selections, for AEAT data sometimes different number of rats were used, indicted as GSF/RIVM) and the observed number of cases.

	Cumulative exposure (WLM)	Exposure rate (WL)	Age at first exposure (month)	Number of rats	Predicted nb of cases GSF-IP	Predicted nb of cases RIVM	Number of cases observed
NEW CEA DATA	0	0	-	120	1.02	0.79	0
	0 / 0.36	0 / 0.09	3	120	0.70	0.57	0
	42	2.44 / 1.72	3	211	4.57	4.42	3
	100	2.25 / 2.12	3	240	9.51	7.86	11
	100	10.1 / 8.40	3	240	9.77	11.15	9
	100	26.6 / 25.30	13	120	2.66	3.21	2
	105	32.2 / 26.31	3	240	9.79	12.11	16
	107	10.3 / 9.01	3	240	12.81	13.09	7
AEAT DATA	0	0	-	499/498	2.82	2.26	1
	100	15	3	198	6.65	7.37	5
	100	150	3	200	5.28	6.41	5
	100	1000	3	196/199	3.84	5.27	3
	200	1000	3	162/166	4.03	7.54	8
	400	1000	4-13	133/120	4.47	5.29	1
	800	1000	9	107/112	6.14	8.84	2
	1000	250	3	54	10.15	12.17	8
	1000	500	3	50	9.13	11.28	3
	1000	1000	3	50	6.79	6.86	7
	1000	2000	4	56	4.30	4.46	10
	1600	1000	9-12	105/115	8.56	11.71	7
	3200	1000	9-12	34/42	6.14	8.39	6

The obtained model fit can be used to make predictions for probability of tumour induction, risks and hazards. Examples are shown in Figures WP5.3 and WP5.4. Figure WP5.3 shows the probability of tumour induction against age as predicted by the RIVM and GSF-IP models for five different exposure patterns (including no exposure) that are representative for the rat data. It is clear from this figure that

higher total exposure leads to a higher probability for tumour development, which can be substantially larger than the natural background. Apart from that, the two 250 WL lines show that there is a strong age-at-exposure effect. Not deducible from this figure is the finding that for the RIVM solution the probability for tumour induction has a maximum around 5-10 WLM/day (for the same total exposure), corresponding to about 35-70 WL. This partly explains the high probability for tumour induction for the 60 WL curve.

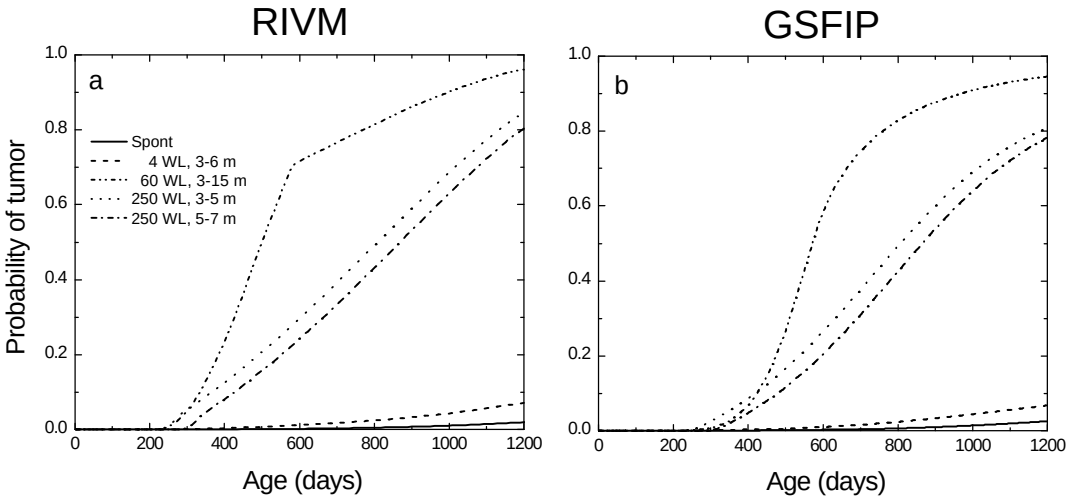

Fig. WP5.3: Probability of tumour induction against age as predicted by the RIVM (a) and GSF-IP (b) models for different exposure patterns.

Similarly, Figure WP5.4 shows the predictions of the RIVM and GSF-IP models for hazard and relative risk against age for a typical exposure pattern (namely 50 WL for 20 weeks from 3 months of age). The background hazard is seen to increase throughout the lifetime of the rat and the exposure to radon adds very significantly to that background. The relative risk (ratio of the hazard curves) increases steeply from start of exposure + t_{lag} up to an age of approximately 350 days (end of exposure + t_{lag}), and decreases for higher ages.

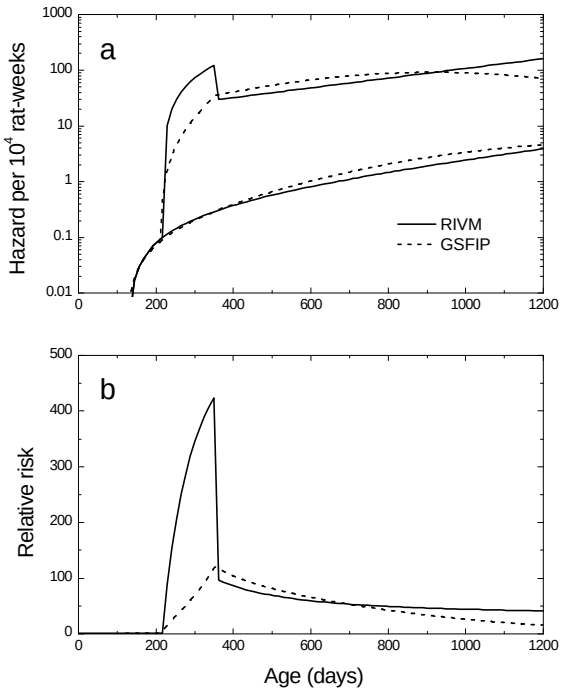

Fig. WP5.4: Hazard (panel a) and relative risk predictions (panel b) for tumour induction of the GSF-IP and RIVM models for an exposure to 50 WL during 20 weeks and starting at 3 months of age. Bottom lines in panel a represent background.

GSF: At PNNL, CEA and AEA, rats have been exposed to radon at different doses and dose rates as a model for radon-exposed humans such as uranium miners. A total of 9913 rats have been analysed by pathologists with classification schemes for both incidental *and* fatal lung tumours. They are classified into a sub-group of incidental tumours if they meet certain criteria of size and appearance. The joint data set comprises 689 rats with at least one lung tumour of which 302 rats had at least one fatal tumour. The risk analysis was done with the IP and IT versions of the TSCE model, which have already been used on recorded and simulated radon-exposed rat data (see §2.1.1). The first objective of the analysis was to establish criteria that allow the pooling of data sets from different laboratories. This must be done with caution if the deviance of the pooled data set is significantly higher than the sum of the deviances from separate data sets. For fatal tumours the data sets of PNNL and AEAT fit together well. However, for the CEA rats the cases, which are predicted in different exposure groups from the TSCE model for the joint data set, do not match the observed cases with acceptable accuracy. Nevertheless, we continued our analysis with the joint data set to assess the separability of the IP and IT versions of the TSCE model. Our results confirm the findings of Kaiser and Heidenreich [2002], which were partly based on simulated rather than real data sets. Judged by the difference of the deviance of the IP and the IT models they are well separable for fatal tumours and less separable for incidental tumours. This work is being prepared for publication [Kaiser et al., 2003, in preparation].

Another piece of work relating to methodological issues examined a method for age adjustment in experimental animal data. Indeed, lung cancers in humans are fatal when untreated, while for rats they can be fatal or incidental. A quantity useful for comparison, and calculable in all contexts is the fraction of all members in a given cohort who develop lung cancer. In animal experiments the age at death may differ considerable among the various treatment groups. Therefore, the value of the observed incidence of cancer does not accurately reflect the tumorigenic effectiveness of the exposure. Age adjustment has to be used to adjust the incidence values to those that presumably would have been observed. New procedures for age-adjustment are proposed for both fatal and incidental cancers adapted to the situation found in radon experiments. These techniques have been applied to several historic and new data sets on lung cancer of radon exposed rats. From the age-adjusted fractions, the lifetime relative and absolute risk can be calculated. This work is being prepared for publication [Heidenreich et al., in preparation].

2.2 Application of mechanistic models to epidemiological data

2.2.1 Analysis of historic miner data

RIVM : Using a previous TMC model derived from analysis of lung cancers induced by smoking and radon exposure in the Colorado miner cohort [Leenhouts 1999], the numbers of lung cancers in the Netherlands and Sweden attributable to smoking and radon were calculated. With the model solution, both for males and for females the lung cancer risk in 1995 was calculated from the smoking habits and radon exposure for the population. The age dependent mortality rate caused by smoking and radon could account for 70% to 90% of the registered lung cancer deaths, dependent on sex and country. The estimates for the radon-attributable fraction are about 4% for the Netherlands and 20% for Sweden. This analysis has been published in a scientific paper [Leenhouts and Brugmans 2001].

GSF: A risk analysis for lung cancer was carried out on tin miners from the Yunnan province in southern China with occupational exposure to radon and arsenic. Additional exposure came from cigarette and pipe smoke. The analysis was based on the complete lifetime records of 12 011 male workers that were available in the follow-up period from 1976-84. For this cohort 842 cancer deaths have been registered.

After eliminating some insignificant parameters the so-called Model B (12 parameters plus a single value for the lag time between malignant conversion and death) [Hazelton 2001] and the Final Model (12 parameters plus two for a gamma-like lag time distribution) were used to produce the results. The models yielded several times higher background promotion rates than observed for lung cancer in other cohorts e.g. the Colorado Plateau uranium miner's cohort. For the dose response of the parameters the best fits were achieved with power law dependence. All three carcinogen agents appear

to affect malignant conversion with smaller effect on initiation. Both arsenic and radon increase the cell promotion, unlike smoking. We found a significant birth cohort effect on the initiation, even after controlling for tobacco use, which is best modelled by a sigmoidal function centred around 1931. For comparison, the Colorado Plateau uranium miner's cohort exposed to radon and smoking showed a birth cohort effect with a linear function. With the Final Model the mortality attributable to radon, arsenic and tobacco exposures alone or to the interaction of two agents was calculated. This analysis has been published [Hazelton 2001].

The recorded exposure history of miner's cohorts contains many uncertainties from systematic bias or from statistical fluctuations. A systematic bias can easily be corrected in the resulting risk. Statistical fluctuations, however, do not only affect the risk uncertainties but also the point estimate of risk. A special likelihood technique that can correct both classical and Berkson errors has been used for the TSCE model with simulated cohort data. The individual beginning and end of exposure were assumed to be exactly known but the dose rate of exposure was given a value from a log-normal distribution. The technique was then applied to a data set of 3236 radon-exposed Colorado miners with 352 lung tumours. Each recorded dose was replaced by a value drawn from a lognormal distribution with various geometric standard deviations. Earlier work with this data set suggested a strong promoting action of radon. This conjecture survived the uncertainty analysis since the dose response function of promotion could be retrieved from uncertain exposure rates with only small deviations. This analysis has been published [Heidenreich 2003].

Some related work has also been carried out comparing regression methods for the TSCE model. In the statistical analysis of cohort data with risk estimation models, both Poisson and individual likelihood regression are widely used methods of parameter estimation. Their performance has been tested with the TSCE model. To exclude inevitable uncertainties of experimental data, cohorts with simple individual exposure history have been created by Monte Carlo simulation. To resemble some properties of atomic bomb survivors and radon-exposed mine workers both acute and protracted exposure patterns have been generated. Then the capacity of the two regression methods has been compared to retrieve *a-priori* known model parameters from the simulated cohort data. For simple models with smooth hazard functions, the parameter estimates from both methods come close to their true values. However, for models with strongly discontinuous functions, which are generated by the cell mutation process of transformation, the Poisson regression method fails to produce reliable estimates. This behaviour is explained by the construction of class averages during data stratification. Hereby, some indispensable information on the individual exposure history is destroyed. It could not be repaired by countermeasures such as the refinement of Poisson classes or a more adequate choice of Poisson groups. Although this choice might exist we were unable to discover it. In contrast to that, the individual likelihood regression technique was found to work reliably for all considered versions of the TSCE model. This work has been accepted for publication [Kaiser and Heidenreich 2003].

2.2.2 Analysis of new French and Czech miner data

The data used for mechanistic modelling were obtained from WP1. The cohort of French miners used for mechanistic modelling includes 5098 miners with 125 lung cancer deaths. From the Czech miners, individual data for 5002 miners are used, based on the sub cohort S52 (2552 miners from the S-cohort exposed since 1952) and miners from the N cohort exposed for at least 4 years. A total of 449 lung cancer deaths have been observed in these data.

RIVM: Fits with the TMC model to these data revealed the following. The exposures in the data sets are not sufficiently high to detect the values for the cell killing parameters (p_i in Eq WP5.1), thus the effect of radon is limited to two parameters (a_1 and a_2) in the model fits. On statistical grounds, the French and Czech miner data can be described with the same set of radiation parameters (a_1, a_2, see Eq WP5.1), if different values for the baseline parameters (μ_{bg} and a) are allowed for the two data sets to describe the different baseline lung cancer mortality rates. The parameter fitted values for a_1 and a_2 are insensitive to incorporation of the slowing down of cellular activity function (see above), or incorporation of a birth-year effect. The relative exposure rate dependency of the fitted parameters is indicated in figure WP5.5. The corresponding doubling doses for the two mutational steps are listed in

table WP5.3. Both in the RIVM and for the GSF model solutions the radon effect on the first mutational step is one order of magnitude larger than that of the second mutational step. From figure WP5.5 it is clear that in comparison with the model fits by GSF, the RIVM fits have larger radon effects on both mutation rates because there is no radiation dependence on the clonal growth of intermediate cells.

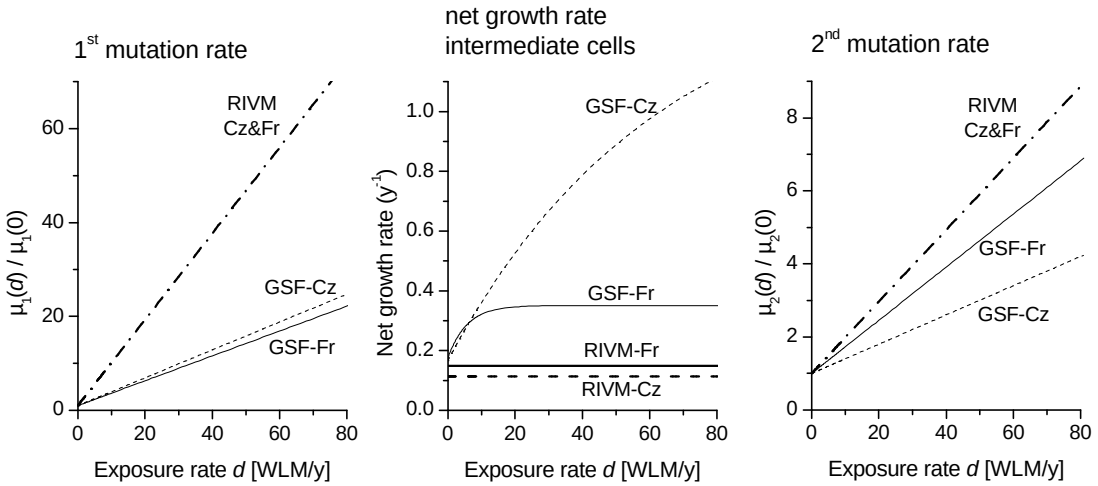

Fig. WP5.5: Fitted dose-dependencies for the model parameters of the different model solutions. The RIVM solution is a joint fit to the French and Czech data sets with the same coefficients for the radon effect. The background values for both data sets, however, are different. The GSF solution results in 2 separate fits.

Table WP5.3: Doubling exposure rates that correspond to the fitted radiation coefficients for the first and second mutational step in the model. 68% confidence intervals are indicated in brackets.

Doubling exposure rates (WLM/y)	RIVM Fr & Cz	GSF Fr	 Cz
First mutation rate	1.1 (0.9-1.3)	3.8 (1.3-50)	3.3 (2.3-5.6)
Second mutation rate	10.2 (7.9-13.2)	14 (7-33)	20 (16-50)

The age-dependent baseline cancer mortality rates that follow from the model solutions to both data sets are plotted in figure WP5.6. The Czech baseline cancer risk is significantly higher than that of the French miners. It should be noted that the effect of smoking is included in the baseline hazard of the model. The effect of the slowing down of cellular activity at very advanced ages in the RIVM model is obvious from the maximum in the hazard at about 74 y, a feature that cannot be captured by the GSF-model. In addition, it is clear that the fitted baseline risks by the RIVM model solutions are larger than that of GSF.

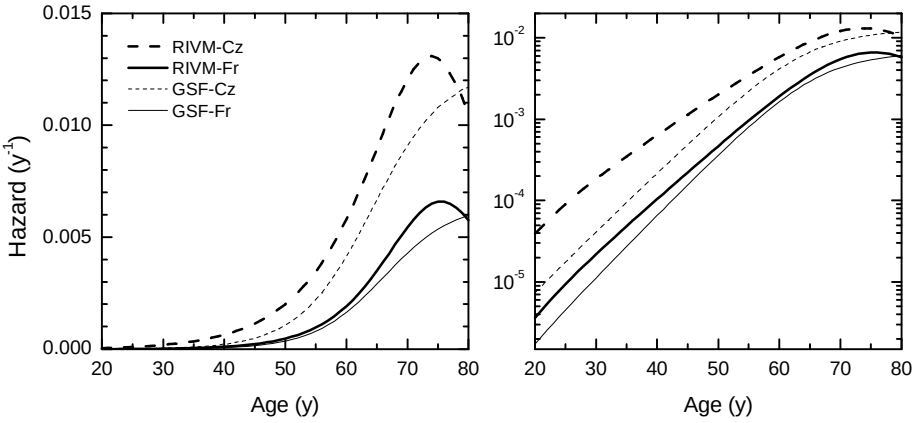

Fig. WP5.6: Age-dependent baseline lung cancer mortality risks resulting from different model fits on a linear (left) and semi-logarithmic (right) scale.

With the model solutions, age-dependent relative risk functions can be calculated for model exposures, see figure WP5.7. In the preferred RIVM model solution there is a uniform effect of radon for both data sets, but the relative risk depends on the baseline risk that is different for Czech and French miners (see Fig.WP5.6). The relative risks for the Czech miners are higher than for the French miners, because the value for the net clonal expansion rate is lower for the former data set (Fig. WP5.5), while the effect of radon in the model is taken relative to the background mutation rates (Eq WP5.1). The sudden decrease of the relative risk curves at t_{lag} after the end of exposure is due to the (instantaneous) radiation effect on the second mutation rate in the model, in combination with a fixed lag time. A distribution for the lag time would smear out this sudden decrease and would be more realistic, but this distribution is not known and cannot be detected from the data. The uncertainties in the calculated risks, resulting from statistical uncertainties of the fitted parameter values for the radiation coefficients as well as for the background parameters, are of the order of ±30% (90% confidence interval) for the RIVM model fits.

From figure WP5.7 it is clear that the relative risks calculated with the RIVM model solutions are considerably lower than those of the GSF solutions. This relates to the higher baseline cancer risks in the RIVM model than in the GSF models (Fig.WP5.6). Multistage models describe the absolute cancer risks in a cohort by a background process that is affected by radiation. In the RIVM solution, which has the merit that it describes both data sets with the same radon effect that is based on radiobiological dose-response relationships, a larger proportion of the lung tumours is attributed to the background instead of the radiation effect.

Dose-rate and protraction effects

From the RIVM model fit to the rat data, an “inverse dose rate” effect follows for exposure rates larger than 5-10 WLM/day. This is mainly due to the maximum in the second mutation at around 10 WLM/day. For higher dose rates the second mutation rate decreases with exposure rate due to a decreased survival of mutations from cell killing. For the miner data the cell killing coefficient cannot be estimated due to the low exposure levels. In absence of this cell killing term, a small direct dose rate effect follows from the RIVM miner solution, due to the small radon effect of the second mutational step in addition to the strong linear effect on the first step. To estimate to what extent the RIVM model description of the French and Czech miner data would allow a cell killing term in the second mutation rate, the maximum value of p_2 (see Eq WP5.1) that can be achieved within the 90% confidence interval of the preferred model fit has been determined. This results in parameter values p_2 = 0.0245 year/WLM and a_2 = 0.147 year/WLM, which yields an exposure rate dependence of μ_2 that has a maximum at about 30 WLM/year. This implies that according to the mechanistic modelling analyses of RIVM, an inverse dose rate effect for dose rates > 30 WLM/year for humans cannot be excluded from the data.

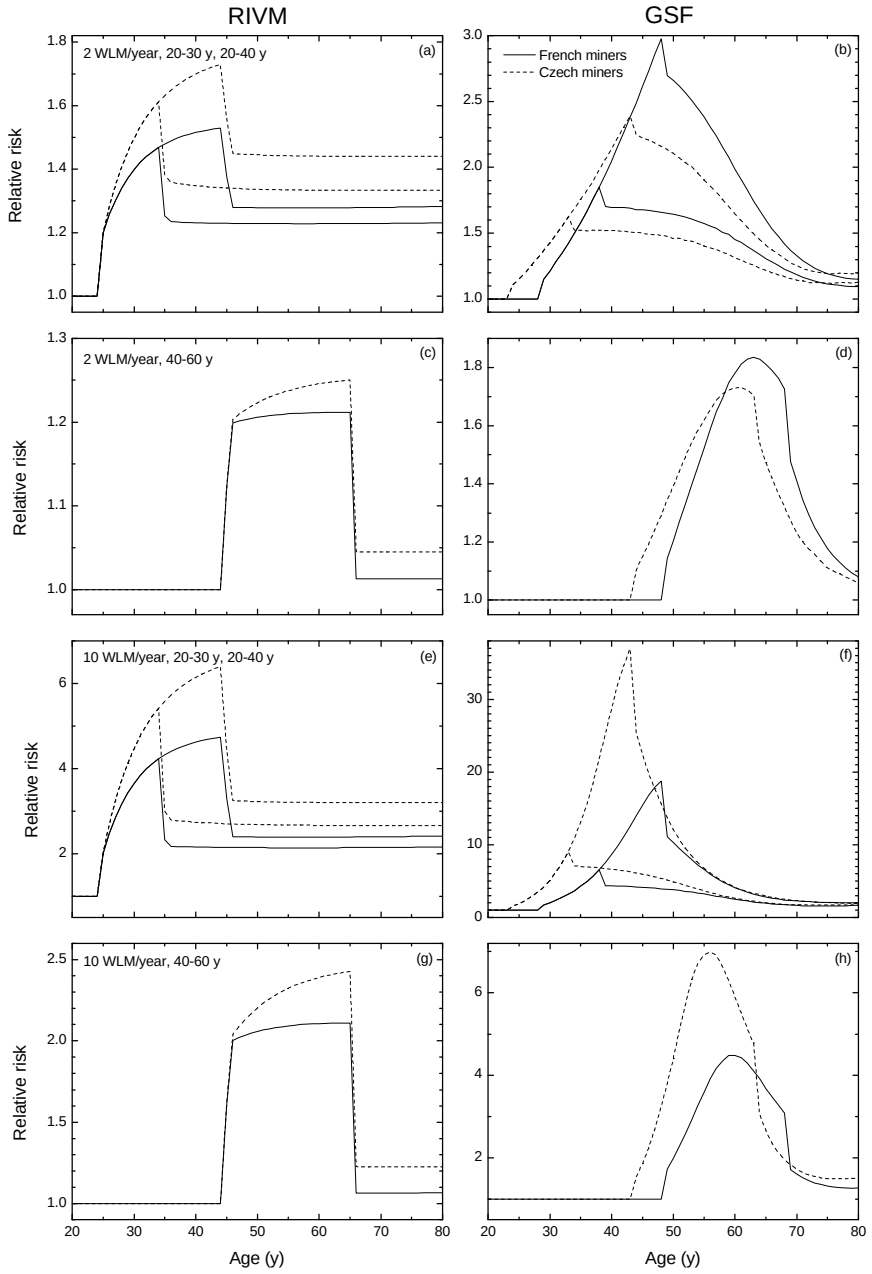

Fig. WP5.7: Age-dependent relative hazard curves calculated from the different preferred models of RIVM (left) and GSF (right) for several exposure patterns (indicated in the left panels). The model calculation for the fit to the French miners is represented by solid lines, the dashed lines are calculated from the Czech miner solution.

A manuscript for a scientific paper on this work is in preparation [Brugmans 2003], and an abstract has been submitted to the IRPA-11 conference.

GSF: Identical versions of the TSCE model are used to analyse lung cancer in historical data from China and the Colorado Plateau and from new data from the Czech Republic and France. An action of radiation on initiation, promotion, and transformation is allowed. While all four data sets indicate a highly significant action of radiation on promotion, the action on initiation is not significant in the French cohort, and barely significant in the Colorado Plateau miners. No action on transformation is found in the Colorado Plateau miners, while the other data sets indicate a borderline significance. The TSCE model can describe all the data sets adequately, but with different model parameters. The observed patterns in exposure, time since start of exposure, birth year, age and calendar year are reproduced well. The doubling exposure rate for initiation is about 3.5 WLM/y in the new data sets, while it is higher in the historic data sets. For transformation the doubling rate is about 20 WLM/y for

the new data sets, while again the historic data give higher estimates. The action of radiation on promotion is quite different in the four data sets. The lag time is much shorter (about 3.5 years) in the Czech data set, compared to about 9 years in the others. These differences also induce different risk estimates at low exposures. The larger power of the new data at these low exposures, compared to the historic data requires less extrapolation. But it has to be kept in mind that at the comparatively low relative risks, even a small correlation between smoking and radon exposure can have strong effects. Therefore smoking information in these data sets would be desirable. This work has been written up and will be submitted for publication [Heidenreich and Tomasek].

2.3 Investigation of the case-control approach to the analysis of epidemiological data using mechanistic model

NRPB has investigated the fitting of the mechanistic model to data on lung cancer among case-control subsets of the cohort of Colorado Plateau uranium miners and a cohort of Czech uranium miners (the latter provided by partner 3). The former dataset was selected as it contains information not only on each subject's occupational exposure to radon but also on his smoking habits. The latter dataset does not have smoking information but does include better quality radon exposure data.

For the Colorado Plateau miners cohort, NRPB has examined how the treatment of prior hard rock mining information in the dataset affects the fitting of mechanistic models. The cohort contains information not only on radon exposures received during uranium mining but also on the total radon exposure received during 'prior' hard rock mining. The component of exposure received from hard rock mining has been ignored in many previous analyses. However, the proportion of the total radon exposure received from hard rock mining varied widely between individuals and, for a considerable number of miners, it contributed a significant proportion of their total exposure (Table WP5.4).

Table WP5.4: Details of the proportion of the total exposure derived from hard rock mining among Colorado Plateau miners.

Hard rock proportion (%)	Number of eligible miners	Proportion of all eligible miners
> 75	44	1.3%
51-75	65	2.0%
26-50	121	3.7%
10-25	247	7.6%
< 0 – 9	777	23.8%
0	2008	61.5%

Unfortunately information on the temporal distribution of this exposure was not provided. After investigation this exposure was considered sufficiently important to be included in all further analyses by assuming that it was all received prior to the start of uranium mining. It was concluded that this was a more appropriate treatment of hard rock mining exposures, rather than ignoring them altogether.

NRPB then investigated the viability of performing analyses on nested case-control data selected from the Colorado Plateau miners dataset and also from the Czech miners cohort, as provided by Partner 3. The ability to obtain results from nested case-control subsets of the miners data that are comparable to those that might be obtained from the analysis of the whole cohort is highly desirable as collecting detailed information on subjects in a case-control subset of a cohort would be cheaper easier than collecting this information from all the subjects in a cohort.

A number of nested case-control datasets were selected with between 2 and 15 controls per case. However, fitting the mechanistic model to these datasets was problematical. In particular, it was difficult to obtain stable reliable maximum likelihood estimates of the parameter estimates of the models. A number of possible reasons for this were identified. Firstly, the quality of information in the Colorado Plateau miners dataset is poor due to the hard rock data problem (as discussed above) and the poor quality of the radon measurements in the mines (particularly in the early years) and the poor smoking information. Secondly, the particular formulation of the two-mutation model of Moolgavkar, Venzon and Knudson (MVK) that was used may have been unsuitable. Thirdly, there may have been a

failure by the software used to fit the models, i.e. the software routine used to maximise the likelihood function did not converge to the true maximum.

Despite these problems a best fitting model was selected containing an effect of radon on the first mutation rate M(0), and separate effects on the growth and death rates, g and d respectively, of the intermediate cells. An effect of smoking on the growth of the intermediate cells was also included. A further problem then occurred, as some of the parameters in this model did not take plausible values for the model to be interpreted mechanistically. The possibility that this was as a result of determining the baseline parameters from the case-control fit was tested by fixing the baseline parameters to values derived from the cohort fit. This approach resulted in more plausible values for the remaining parameters (Table WP5.5).

Table WP5.5 : The parameter values of the best fitting model for the Colorado Plateau data

	Case-control model all parameters fitted	Cohort model all parameters fitted	Case-control model with baseline parameters fixed at cohort values
Model deviance	1366.56	3872.23	1393.53
Radon effects parameters (WLM/month)			
R x M(0)	9.56E-03	-8.23E-03	5.32E-8
R x g	-2.09E+03	2.19E-04	3.1924
R x d	-1.16E+01	-3.10E-03	3.1907
Smoking effects parameters (Packs per day)			
S x g	4.15E-04	5.20E-05	6.47E-5
Background parameters			
g	1.99E-02	1.23E-01	1.23E-01
d	1.51E-01	8.05E-02	8.05E-02
M(0), M(1)	3.69E-02	8.10E-07	8.10E-07

R: radon effect; S: smoking effect; M(0): first mutation rate; M(1): second mutation rate; g: growth rate; d: death rate.

The above investigation was repeated using the Czech miners data. As this dataset did not contain any smoking information, the number of possible models that could be fitted was much fewer, only 16. All these models were fitted and the best (in terms of minimum deviance) selected. This best model contained effects of radon on the first and second mutation rates and the death and differentiation rates of the intermediate cells. As with the model derived from the Colorado Plateau miners data there were problems with the mechanistic interpretation of the coefficient values. The model was refitted using fixed baseline parameter estimates derived from fitting the same model to the full cohort but the resulting parameter values still did not suggest a mechanistic interpretation of the model (Table WP5.6).

Table WP5.6: Czech miners: The parameter values of the full model, based on 15 controls per case, and for the full model based on the cohort data.

Parameter	Value from the case-control fit	Value from the cohort fit
Radon parameters (WLM^{-1})		
R x g	-9.16	-12.65
R x d	-1.42	9.25E-06
R x M(0)	0.00170	2.38E-06
R x M(1)	0.000133	2.16E-08
Background parameters		
g	0.808	0.0724
d	0.802	1.979E-06
M(0), M(1)	0.00187	6.935E-07

R: radon effect; S: smoking effect; M(0): first mutation rate; M(1): second mutation rate; g: growth rate; d: death rate.

The fitting of the mechanistic models to case-control subsets of these two cohorts has not produced reliable results in terms of showing what stages of the model radon and smoking are affecting. We conclude that there are three possible causes for this. Firstly, the data were in some way incompatible with this type of model possibly because they did not contain sufficient information, secondly, the formulation of the model that was used was not appropriate, or thirdly, the model fitting software was at fault. To determine which of these was correct was not possible within the time frame of this contract. Thus it is not possible to recommend that fitting case-control subsets of data from these miners cohorts is a viable option until the problems described above have either been explained and/or overcome. This work has been written up in two parts, the first of which has been accepted for publication while the second has yet to be submitted [Haylock and Muirhead a-b].

3. MAIN ACHIEVEMENTS

Description of the mechanistic modelling of animal data

Separate fits to the historic PNNL and CEA rat data yielded similar fitted parameter values with a near linear dose-response relationship for the first mutation rate and a linear dose response relationship for the second mutation rate with an exponential cell killing term. The linear low-dose term for the second mutation rate is an order of magnitude less than that of the first mutation rate. A joint model was fitted to both datasets simultaneously without loss of statistical significance. However, two different forms of the model, the initiation-transformation form and the initiation-promotion form could both describe the data on incident tumours equally well, although a difference could be seen if the analysis was restricted to fatal tumours.

Non-lung cancer mortality risks were examined and found to be dependent more on exposure rate rather than cumulative exposure, up to very high exposures.

The feasibility of pooling the historic PNNL and CEA rat data and the new CEA and AEAT rat data and thus increasing the overall statistical power was examined. If all tumours were considered incidental then although it was statistically significantly better to model some groups separately, a joint fit of all the data (more than 12 000 rats) provided a reasonably good fit. The model obtained clearly indicates that higher total exposure leads to a higher probability of tumour development and a strong age-at-exposure effect. A maximum probability for tumour induction was found with an exposure of 5-10 WLM/day with a corresponding total exposure of between 35 and 70 WL.

Description of the mechanistic modelling of historic miner data

A dataset on Chinese tin miners occupationally exposed radon and arsenic was analysed. The models yielded several times higher background promotion rates than observed for lung cancer in the Colorado uranium miner cohort. For the dose response of the parameters the best fits were achieved with power law dependence. Radon, arsenic and smoking all appear to affect malignant conversion with smaller effect on initiation, while only arsenic and radon increase the cell promotion. A significant birth cohort effect on the initiation was identified even after controlling for tobacco use.

The possibility of using a case-control form of the mechanistic model in which case-control subsets would be selected from of miners cohorts was investigated. The best fitting model fitted to case-control subsets of the historic Colorado Plateau miners data did not have the same form as that obtained from the full cohort. The fitting of case-control models based on data selected from the Czech miners cohort has also been investigated but as yet has not proved successful. It was concluded that the case-control approach could not be relied upon to analyse the currently available data.

Estimates of the radon attributable fraction of lung cancer incidence were calculated for the population of the Netherlands and Sweden. Radon exposure and smoking was estimated to account for between 70 and 90% of the registered lung cancer deaths. The radon attributable component was estimated to be about 4% for the Netherlands and 20% for Sweden.

Description of the mechanistic model fitted to the new French and Czech miner data

These datasets were analysed both separately and jointly by RIVM and GSF. The magnitude of the radon effect on the different model steps depends on the assumptions made in the modelling, e.g. whether radon influences the proliferation of intermediate cells at low exposures or not. However, both groups found that the effects of radon on the first mutation rate were an order of magnitude greater than its effect on the second mutation rate. The effects of radon were also found to be linear over the range of exposures covered by the data. RIVM found that the French and Czech datasets could be pooled and modelled together if separate baseline risks were incorporated into the model.

The GSF analyses found that for the historic and new human datasets there was a highly significant effect of radon on promotion. However, this effect varied between the datasets in that the lag time was found to be only 3.5 years in the Czech miners compared with 9 years for the other datasets. The effect of radon on initiation was also significant except for the French cohort, while there was an effect on the transformation stage for all except the Colorado miners cohort. However, in all instances the TSCE model was found to adequately reproduce the observed patterns in exposure, time since start of exposure, birth year, age and calendar year.

Two other pieces of work relating to methodological issues were carried out. The first concerned a method for comparing the performance of Poisson and individual likelihood regression methods for fitting the two stage clonal expansion model. The second examined a method for age adjustment in experimental animal data to overcome the problem that because the age at death of animals may vary significantly between treatment groups, the observed incidence of cancer may not reflect the actual effectiveness of the exposure.

PUBLICATIONS AND SCIENTIFIC COMMUNICATIONS

Bijwaard H, Brugmans MJP, and Leenhouts HP, A consistent two-mutation model of lung cancer for different data sets of radon-exposed rats, *Radiation and Environmental Biophysics* 2001; 40: 269-277.

Brugmans MJP, Rispens SM, Bijwaard H, Laurier D, Rogel A, Tomášek L, Tirmarche M. Multistage model description of French and Czech miner data: implications for radon-induced lung cancer risks. Abstract submitted to *IRPA-11 conference*.

Brugmans MJP, Rispens SM, Bijwaard H, Laurier D, Rogel A, Tomášek L, Tirmarche M. Radon-induced lung cancer in French and Czech miner cohorts described with a two-mutation cancer model, in preparation.

Haylock RGE, Muirhead CR, Fitting the two stage model of carcinogenesis to nested case–control data on the Colorado Plateau uranium miners: Dependence on data assumptions. *Radiation and Environmental Biophysics*, accepted

Haylock RGE, Muirhead CR, Fitting the two stage model of carcinogenesis based on a nested case–control analysis of lung cancer in Czech uranium miners. In preparation.

Hazelton WD, Luebeck GE, Heidenreich WF and Moolgavkar SH. Analysis of a historical cohort of Chines tin miners with arsenic, radon, cigarette smoke and pipe smoke exposures using the biologically based two-stage clonal expansion model, *Radiation Research* 2001; 156: 78-94.

Heidenreich WF, Luebeck GE and Moolgavkar SH. (2003) Effects of exposure uncertainties in the TSCE model, and application to the Colorado miners data. Accepted *Radiation Research*

Heidenreich WF, Cross FT, and Paretzke HG. Life expectancy of rats exposed to radon. Submitted to *Radiation Research*

Heidenreich WF, Tomasek L, Rogel A, Laurier D, Tirmarche M. Studies of radon-exposed miners in the Czech Republic and France, using a biologically based model; comparison with historic data from China and the Colorado Plateau. In preparation.

Heidenreich WF, Morlier JP, Monchaux G. Interaction of smoking and radon in rats: a biologically based mechanistic model. In preparation.

Heidenreich WF, Morlier JP, Collier C, and Monchaux G. Age-adjustment in experimental animal data and its application to lung cancer in radon exposed rats. In preparation

Kaiser JC and Heidenreich WF Identifying dose dependencies of the two-stage clonal expansion model with simulated cohorts. *J. Radiol. Prot.* 2002; 22: A57-A60

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Kaiser JC, Heidenreich WF, Morlier JP, Monchaux G, and Collier C. Joint analysis of the lung tumour risk in radon-exposed rats from different experiments with mechanistic models In preparation.

Leenhouts HP and Brugmans MJP, Calculation of the 1995 lung cancer incidence in the Netherlands and Sweden caused by smoking and radon: risk implications for radon, *Radiation and Environmental Biophysics* 2001; 40: 11-21

WORK-PACKAGE 6: SYNTHESIS OF RESULTS FROM HUMAN AND ANIMAL DATA

Principal contractor: IRSN, D. Laurier
Participants: All partners

A large number of studies concerning miners cohorts or animal experiments have been published. They demonstrate an excess risk of lung cancer death associated with radon exposure. However a large proportion of these results are based on high radon exposures, received during a short period of exposure.
Our collaborative work has been conducted within the 5th Framework Programme of the European Community, and aims to provide new knowledge on the effects of radon exposure at a low dose rate and low cumulative exposure. The project involved three different fields of research: epidemiology, animal experiments, and mechanistic modelling. The aim of work-package 6 is to synthesize the results obtained from both human and animal data.

PRODUCTION OF LARGE DATASETS AT LOW EXPOSURE RATE: EPIDEMIOLOGICAL AND ANIMAL DATA

The first four work-packages provided new datasets, both from epidemiology (WP1, WP2 and WP3) and from animal experiments (WP4). Compared to previously existing data, their main interest is to focus on the low exposure range. Figures WP6.1 and WP6.2 illustrate this point by presenting schematically the position of the new data and of the previous data according to cumulative exposure and duration of exposure.

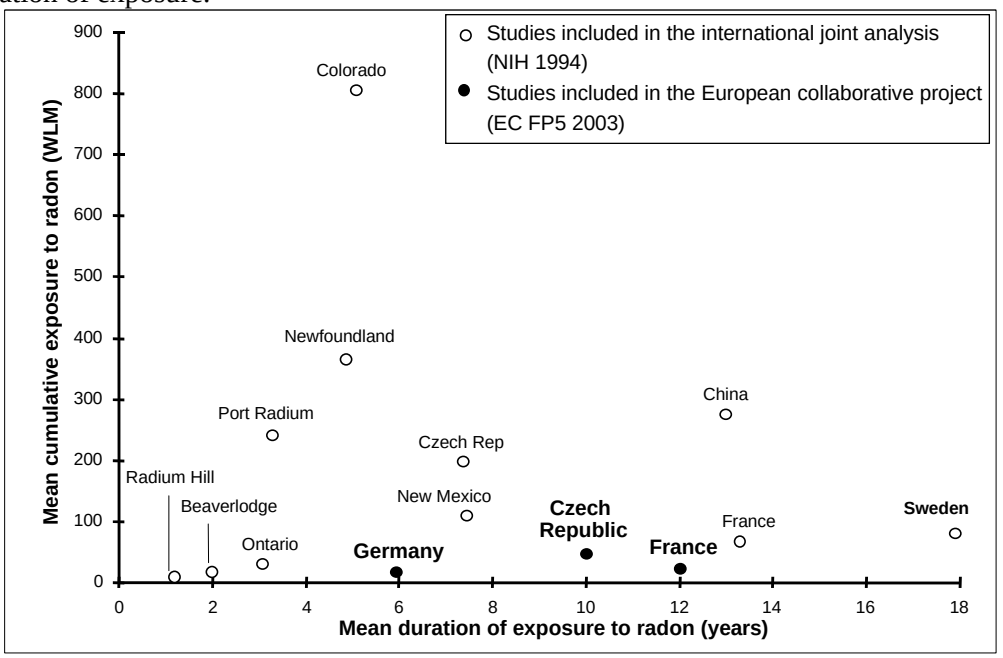

Fig. WP6.1: Miner cohort studies: position of the data provided by WP1 and of previous data, according to duration and cumulative exposure to radon.

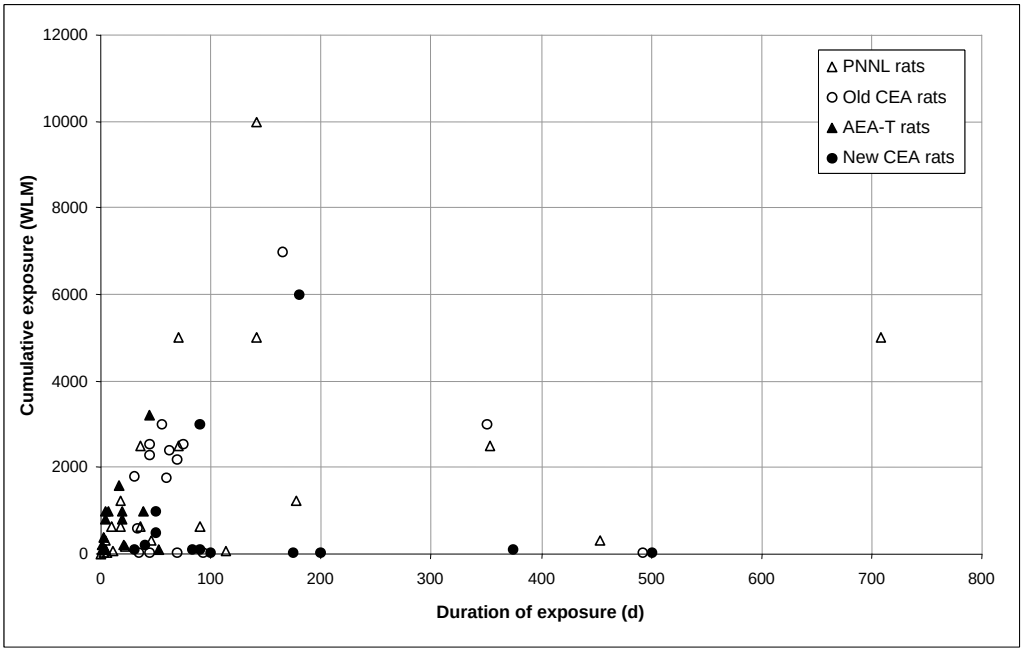

Fig. WP6.2: Animal experiments: position of the data provided by WP4 and of previous data, according to duration and cumulative exposure to radon (PNNL: Pacific Northwest National Laboratory, USA).

WP1 provided data from three cohorts of miners with low levels and long duration of exposure to radon (figure WP6.1). Together, the three cohorts constitute a set of more than 27 000 miners, for a total of more than 550 000 person years of follow-up. Among all miners, 95% accumulated less than 100 WLM (92, 79 and 100% in the French, Czech and German cohorts respectively). As detailed in the WP1 chapter, exposure data have also been collected for other pollutants in the mines (gamma radiation, ore dust, arsenic), which will allow multifactorial analyses of risk in the future.

WP2 and WP3 provided a large dataset to evaluate the joint effect of radon exposure and smoking on the risk of lung cancer among miners. As described in the WP2-3 chapter, the four case-control studies include a total of more than 1600 cases and 3600 controls. In addition, other information was also collected in the German (WP3) case-control study (indoor radon exposure, X-ray diagnosis of silicosis…), which will be considered in further analyses.

WP4 allowed the finalisation of data from experiments that were initiated during the 4th EC FP. A histo-pathological validation of all tumours has been performed, and efforts have been made to distinguish fatal from incidental tumours. In total, more than 4000 rats (plus 1500 non-exposed control rats) have been exposed to various exposure rates and durations of exposure under controlled conditions, and followed-up over their life span (see figure WP6.2).

RESULTS FROM ANIMAL DATA

The data from rat experiments performed by AEA-T and CEA have been analysed in WP4. An important effort has been made to discriminate between incidental and lethal tumours. A standardised and systematic rule has been set up, jointly by AEA-T and CEA, on the basis of information collected during autopsy. One advantage of these data over human data is that they provide estimates on a lifelong follow-up of the animals. The analysis showed that the age at death might differ considerably among the various treatment groups (a reduction of life duration is observed particularly in groups who received very high exposures). Methodological work has been performed by GSF to propose procedures for age-adjustment in the analysis of the risk of both fatal and incidental cancers.

The analysis of the data shows that the risk of fatal lung cancer tumours in rats increases with cumulative exposure and with increasing potential alpha energy concentration (PAEC), i.e., exposure-rate. The highest proportion of squamous cell carcinomas was observed in rats exposed at high PAEC, and decreased with decreasing PAEC. The larger and most invasive tumours were also observed in rats exposed at high PAEC and the size and invasiveness of tumours decreased with decreasing PAEC and/or protraction of exposure. The analysis confirms previous results, showing that at high cumulative exposures, the risk per WLM decreases with increasing PAEC. But in contrast, the results indicate that at lower cumulative exposures of about 100 WLM, the risk per WLM increases with increasing PAEC. These data suggest that the induction of lung cancer is the result of a complex interplay between cumulative exposure and exposure-rate, with an optimal combination of these two parameters (form the available data, LEAR per WLM appears to be maximum for cumulative exposure around 50 to 100 WLM, and PAEC ranging from 50 to 188 WL).

The datasets elaborated by CEA and AEA-T in the frame of WP4 have been provided in a format suitable to the mechanistic modellers (WP5). Mechanistic modelling applied to the animal data aimed to provide a description of the multistage carcinogenesis model implied after chronic alpha exposure. Analyses were carried out to investigate the particular stages of the two stage clonal expansion model on which the effect of radon was strongest. Other data previously investigated (PNNL rats, old CEA experiments) were also included in some analyses, leading to a total number of animals larger than 10 000. The approaches used varied between GSF and RIVM. It was found that both the initiation-transformation form and the initiation-promotion form of the model fitted various datasets equally well when all tumours were assumed to be incidental. The results of the different teams agreed to show a much larger impact of radon exposure on initiation than on the transformation stage. The models also agree in confirming that higher total exposure leads to a higher probability for tumour development, which can be substantially larger than the natural background. Furthermore, from the RIVM model, it was observed that for the same total exposure, the probability for tumour induction has a maximum around 5-10 WLM/day (about 35-70 WL). For larger exposure rates, an “inverse dose rate” effect follows, mainly due to a maximum in the second mutation at around 10 WLM/day (due to a cell killing effect at higher dose rates). These results support a complex effect of exposure rate on the risk of lung tumour associated with radon exposure.

RESULTS FROM EPIDEMIOLOGICAL DATA: ESTIMATED RISK AMONG MINERS

The French cohort of uranium miners includes 5098 miners, followed up to 1994. The total number of person-years is 133 521, for a mean duration of follow-up of more than 26 years. The total number of deaths is 1162, from which 125 died of lung cancer. In order to perform a joint analysis of the data, a selection has been performed from the Czech cohorts of miners for the collaborative project. A cohort of 5002 miners has been constituted, including miners from the S cohort employed since 1952 and miners from the N cohort employed since 1968 for more than 4 years, with follow-up to 1995. The number of person-years is 115 261, for a mean duration of follow-up of more than 23 years. The total number of deaths is 1871, from which 449 died of lung cancer. The joint dataset therefore includes more than 10 000 miners, with a long duration of follow-up and precise information on annual individual exposure to radon, allowing risk analysis in relation to and low cumulative exposures at low exposure rates.

Modelling the exposure-risk relationship: epidemiological approach

The joint analysis performed in WP1 confirms the existence of an increased risk of lung cancer death, associated with cumulative radon exposure. No other pathologies are in significant excess, but elevated risks are observed for leukaemia and kidney cancer, that may need further analyses in the future. The analysis also confirms the modifying effect of time since exposure and age at exposure: the excess relative risk per WLM decreases with increasing time since exposure and with increasing age at exposure. The method of exposure assessment (measured versus retrospectively estimated) also appears to be an important modifying factor, especially in the French cohort, possibly reflecting a

higher degree of measurement error associated with the retrospective reconstruction of exposures. No effect of exposure rate is observed. This result is in agreement with previous analyses performed on restricted ranges of exposure [Lubin 1995, BEIR VI 1999]. But one main facet of our results is that they are based on a population of miners exposed at low annual rates with a complete follow-up over more than 20 years, whereas previous results were based on populations of miners that could receive high levels of exposure, with a truncated follow-up when a given level of cumulative exposure was reached.

Several different methodological approaches were applied in the epidemiological analysis (sliding windows of exposure, continuous or categorical modifiers, consideration of median exposure…). All of the approaches showed a modifying effect of time since exposure or age at exposure, but no effect of exposure rate on the exposure-risk relationship. The model proposed by WP1 takes into account the method of exposure assessment (estimated or measured), and time since median exposure and age at median exposure as continuous modifiers. This model gives a good fit of the data and allows a smooth estimation of the relative risk (model M4, see table WP1.8).

Modelling the exposure-risk relationship: mechanistic approach

The same data have been used in WP5 to estimate the risk of lung cancer death derived from mechanistic modelling. Multistage models describe the absolute cancer risks in a cohort by a background process that is affected by radiation. Different approaches have been used to fit the data: two models separately for the French and Czech cohorts (GSF solution), or a uniform effect of radon for both datasets, but the relative risk depends on the background risk which is higher for the Czech than for the French population (RIVM solution). Both solutions gave a reasonably good fit of the data, and agree with a linear increase of risk with cumulative radon exposure. They also agree in confirming a much larger effect of radon on the first mutational step (initiation) rather than on the second mutational step (transformation) in the process of carcinogenesis. Nevertheless, the solution proposed by GSF supports a significant effect of radon on promotion; however, the effect of radon on initiation is not significant in the French cohort. Depending on the solution, the doubling dose is between 1.1 and 3.5 WLM/year and between 10 and 20 WLM/year, respectively for the first and the second mutational step. These values are lower than those obtained by previous analyses of historic datasets (Colorado miners).

Due to the low exposure levels among the Czech and French miners, a cell killing coefficient cannot be estimated. Through the RIVM solution, no noticeable dose rate effect is estimated. Nevertheless, their model analysis shows that an inverse dose rate effect for exposure rates > 30 WLM/year cannot be excluded from the data. Only a small inverse exposure rate effect is predicted from the GSF solutions. The mechanistic modelling was found to adequately reproduce the observed patterns in exposure, time since start of exposure, birth year, age and calendar year.

A methodological work performed by GSF compared the fit of the individual heuristic approach with that of the classical epidemiological approach by Poisson regression: it appears that the fit obtained by mechanistic modelling is as good as the one of the epidemiological approach with a simple linear relationship with cumulative exposure (without taking into account modifying factors). The results of the different teams agreed to show a much larger impact of radon on initiation than on the transformation stage.

Comparison of the results from the different approaches

Figure WP6.3 illustrates the relative risk predicted by the different models on a specific miner scenario: constant exposure to 2 WLM per year during 20 years, from 20 to 39 years. In addition to the models proposed in WP1 and WP5, the estimated risk according to the two preferred models of the BEIR VI report is also plotted [BEIR VI 1999].

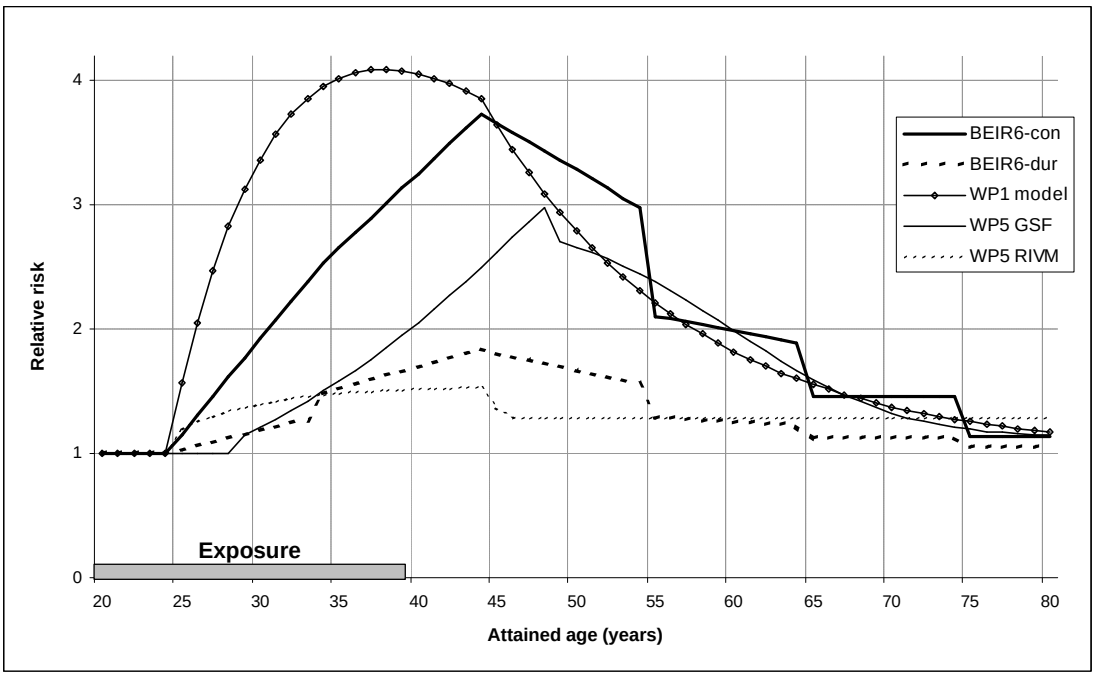

Fig. WP6.3: Relative risk according to age for a constant exposure to 2 WLM per year during 20 years, from 20 to 39 years (scenario S3), estimated by different models.

BEIR6-con and BEI6-dur: BEIR VI "exposure-age-concentration" and "exposure-age-duration" models [BEIR VI 1999, table A.4, p 151] - WP1 model: preferred model from the joint Czech and French analysis (table WP1.8, model M4), with coefficient for "measured exposures" - WP5 GSF: TSCE model estimated by GSF when fitting data from the French miner cohort - WP5 RIVM: TMC model estimated by RIVM

After a period of latency following the beginning of exposure (fixed 5 year lag time for all models, except the GSF model, in which a 9 year latency time is estimated between the occurrence of the first malignant cell and death), all models show an increase of risk during the period of exposure, and then a decrease of relative risk with time since exposure. The proposed solutions appear in agreement with the risk estimated from the BEIR VI models. In the example of figure WP6.3, the minimum risk is predicted by the RIVM model and the highest one by the WP1 preferred model at young ages, but at old ages the situation is inverse and the differences are much smaller. Compared to the BEIR VI models, the model derived from the Czech and French joint analysis allows a smoother estimation of the evolution of the risk with age and time since exposure. The differences between the models proposed by WP1 and WP5 do not appear larger than the difference between the two models proposed by the BEIR VI committee.

In order to facilitate the comparison of the results obtained by the different models, we calculated "Cumulated risks" of lung cancer (CR) [Thomas 1992]. CR is calculated as the sum of the risk of death from lung cancer each year of life i under the condition of surviving age, according to [BEIR VI 1999, p170-171]. Cumulated risk of lung cancer among non-exposed individuals (CR_0) is given by:

$$CR_0 = \int_0^{i\max} r_0(i)\, S_0(i)\, (1-q_0(i)) / p_0(i)\ di \qquad \textit{Eq. WP6.1}$$

where imax = age at which the cumulated lung cancer hazard is estimated,
$r_0(i)$ = mortality rate from lung cancer at age i
$p_0(i)$ = mortality rate from all causes at age i,
$q_0(i)$ = probability of surviving year i given surviving up to year i-1
$= \exp(-p_0(i))$
$S_0(i)$ = probability of surviving up to age i
$= \prod_0^i q_0(k)$

Cumulated risk of lung cancer among individuals with exposure E (CR_E) is calculated using the corresponding probabilities as follows:

$$r_E(i) = r_0(i) + r_0(i)\ ERR_i, \quad \text{and} \quad p_E(i) = p_0(i) + r_0(i)\ ERR_i,$$

where ERR_i is the excess relative risk from exposure E at age i.

Cumulated excess absolute risk (CEAR) is then given by: $CEAR = CR_E - CR_0$,
and Cumulated excess relative risk (CERR) is calculated as: $CERR = CEAR / CR_0$.

For ease of comparison between the estimates obtained by the different models from WP1 and WP5, calculations were made considering only mortality by lung cancer (total mortality was not taken into account). Then :

$$p_0(i) = r_0(i), \qquad q_0(i) = \exp(-r_0(i))$$

$$\text{and} \quad CR_0' = \int_0^{i\max} S_0(i)\ (1-\exp(-r_0(i)))\ di$$

And CR_0' can be approximated by :

$$1-\exp(-IH) \qquad \textit{Eq. WP6.2}$$

where IH = integrated hazard of lung cancer death = $\int_0^{i\max} r_0(i)\ di$

Tables WP6.1 presents the estimated CERR at 70 years obtained by the different models for several scenarios of "miner exposure". Eight scenarios are proposed, with various combinations of concentration (2 or 10 WLM/year), duration (10 or 20 years) and age at exposure (20 or 30 years).

Table WP6.1: Cumulated Excess Relative Risk of lung cancer death at 70 years calculated for several "miners scenarios" using different risk models.

	Exposure				CERR at 70 years									
	age	rate	duration	cumul	BEIR 6 con		BEIR 6 dur		WP1 model		WP5 GSF		WP5 RIVM	
Scenario	(y)	(WLM/y)	(y)	(WLM)	Cz	Fr	Cz	Fr	Cz	Fr	Cz	Fr	Cz	Fr
S1	20 29	2	10	20	0.43	0.45	0.07	0.08	0.39	0.42	0.26	0.35	0.34	0.23
S2	30 39	2	10	20	0.51	0.54	0.09	0.09	0.43	0.45	0.24	0.34	0.11	0.05
S3	20 39	2	20	40	0.94	0.99	0.25	0.27	0.81	0.87	0.52	0.74	0.45	0.29
S4	30 49	2	20	40	1.12	1.14	0.31	0.31	0.87	0.84	0.48	0.71	0.18	0.09
S5	20 29	10	10	100	1.05	1.11	0.35	0.38	1.95	2.11	1.43	1.22	1.69	1.15
S6	30 39	10	10	100	1.26	1.33	0.44	0.47	2.13	2.26	1.23	1.07	0.59	0.28
S7	20 39	10	20	200	2.31	2.44	1.26	1.35	4.08	4.37	3.10	2.81	2.36	1.45
S8	30 49	10	20	200	2.74	2.81	1.53	1.56	4.20	4.33	2.61	2.35	0.99	0.47

CERR calculated using equation WP6.2 ; BEIR 6 con: BEIR VI "exposure-age-concentration" model as published in [BEIR VI 1999, table A.4] ; BEIR 6 dur: BEIR VI "exposure-age-duration" model as published in [BEIR VI 1999, table A.4] ; WP1 model: preferred model from the joint Czech and French analysis (table WP1.8, model M4), with coefficient for measured exposure ; WP5 GSF & WP5 RIVM: models retained by GSF and RIVM, as described in WP5 ; Cz : calculated using Czech cohort specific rates for background lung cancer mortality; Fr : calculated using French cohort specific rates for background lung cancer mortality.

The values of CERR predicted by the different models are very close for scenarios with low cumulative exposures. Differences appear for high cumulative exposures (above 100 WLM). As a first explanation, one has to notice that the WP1 preferred model uses 2 coefficients according to the method of exposure assessment (measured or estimated). In table WP6.1, we used the coefficient related to measured exposures, which corresponds essentially to low levels exposures in the Czech and French cohorts. So it may be that this coefficient leads to an overestimation of risk at high rates of exposure. A second explanation is that the background lung cancer rates estimated by the two mechanistic models are higher than the one used by the epidemiological models (CR_0' at 70 years old

estimated by the WP5 RIVM model, the WP5 GSF model, and the epidemiological models are respectively 0.142, 0.092 and 0.063 for Czech miners, and 0.048, 0.039 and 0.045 for French miners). The predicted CERR are coherent with those predicted by the BEIR VI models. The variations in predicted risk between the WP1 and WP5 models are not larger than those between the BEIR VI "exposure-age-concentration" and "exposure-age-duration" models.

Table WP6.1 allows evaluating the impact of the background rates on the estimated risks. For the two BEIR VI models and the WP1 model, the estimates obtained with the French and Czech data are very close (difference of less than 10%), and CERR do not appear to be sensitive to background rates. But this is not true for CEAR, which are systematically higher with the Czech than with the French data (between 20 and 30% higher). For the two mechanistic models, the differences between the two countries are larger. Note that GSF used two separate models for the French and Czech cohorts, while RIVM ends up with a single estimate of the relative risk associated with exposure combined with different estimates of the background risk for France and the Czech republic. With the GSF model, CEAR are 60 to 170% higher with the Czech than with the French background rates, whereas the ratio of CERR between the two countries is not systematic (0.9 to 1.4 according to the scenario). With the RIVM model, CEAR and CERR are higher with the Czech than with the French background rates.

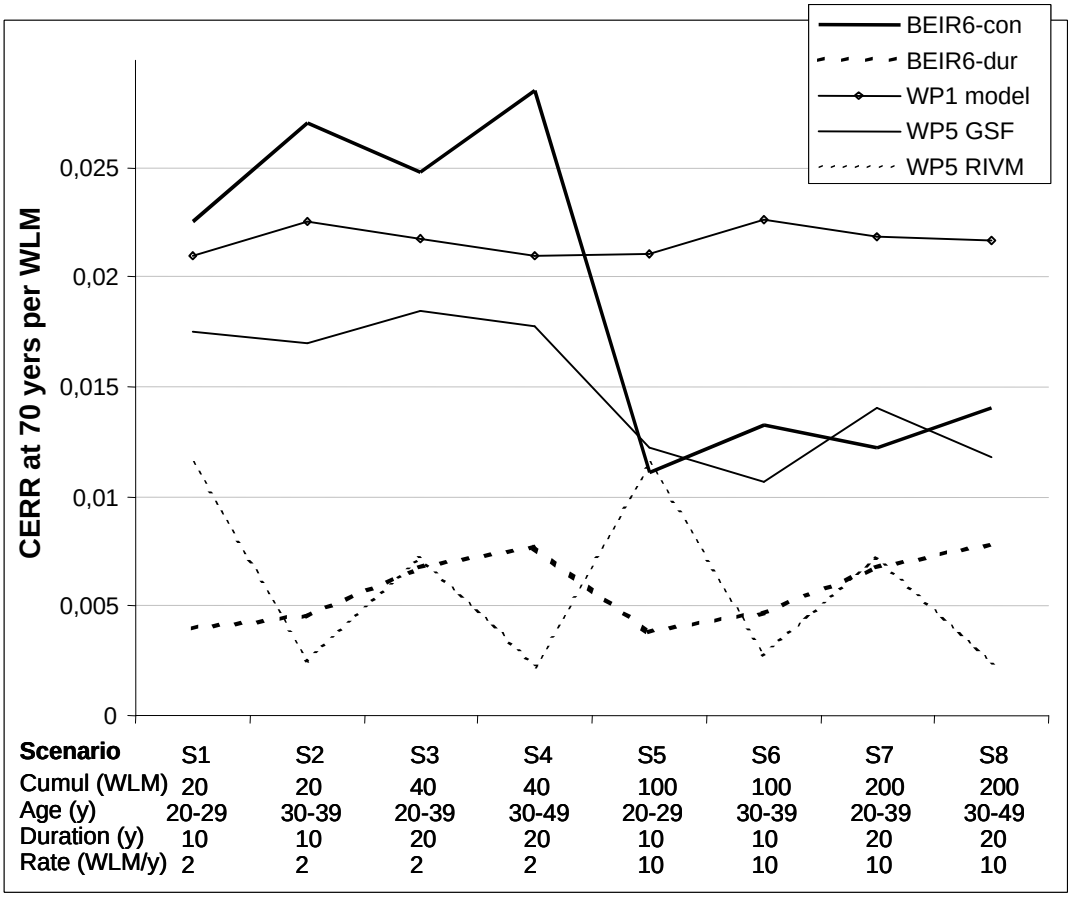

Fig. WP6.4: Cumulated Excess Relative Risk of lung cancer death at 70 years per WLM, calculated for several "miners scenarios".

Calculation used rates from the French cohort of miners as background rates. BEIR 6 con: BEIR VI "exposure-age-concentration" model as published in [BEIR VI 1999, table A.4] ; BEIR 6 dur: BEIR VI "exposure-age-duration" model as published in [BEIR VI 1999, table A.4] ; WP1 model: preferred model from the joint Czech and French analysis (table WP1.8, model M4), with coefficient for measured exposure ; WP5 GSF & WP5 RIVM: models retained by GSF and RIVM, as described in WP5.

Figure WP6.4 compares the CERR obtained by the 5 different models, when divided by the cumulative exposure. CERR vary from 0.002 to 0.028 per WLM, according to scenario and model. The sharp decrease of risk with exposure rate predicted by the BEIR VI "exposure-age-concentration" model can be seen from this figure. A smaller inverse rate effect can also be seen in the results of the

GSF model. No effect of exposure rate is predicted in the RIVM model, but an effect of age at exposure can be seen. CERR per WLM estimated by the WP1 preferred model is almost constant over all scenarios. These results confirm that, at relatively low levels of exposure, no inverse dose rate effect is observed between radon exposure and the risk of lung cancer death.

SYNTHESIS OF RESULTS FROM ANIMAL AND EPIDEMIOLOGICAL DATA

First of all, several differences have to be taken into account before comparing results from human and animal data. The average duration of life among rats is approximately 900 days. This relatively short duration implies generally short exposure periods and elevated rates of exposure. Also, previous studies suggest that rats have a higher sensitivity to radon, for the same level of exposure [Hofmann 1993]. Therefore, levels of exposure and exposure rates have to be considered differently among human and animal data. Another difference is that rats were followed up over their total lifespan until death. In the Czech and French miners cohorts, as the mean age at end of follow-up is 56 and 55 years old, respectively, we are far from a lifetime coverage of risk. Therefore lifetime (or cumulated up to a given age) risk estimates have to be constructed to allow a parallel with the results of animal experiments. If we accept a correspondence for ageing between rats and men of 1 day for 1 month, then 900 days for a rat approximately corresponds to an age of 74 years old for a man. A third important difference lies in the endpoint: rats are not dying of lung cancer, and the occurrence of a lung tumour was diagnosed at necropsy. Among miners, lung cancer is determined as the cause of death on the basis of death certificates, but no information is available on incidence. The elaboration of histopathological criteria to determine the fatality of a tumour among rats was therefore a key step to allow a comparison of risk estimates between animal and human data. Given all these restrictions, the following results have to be underlined from the present research project.

Epidemiological results obtained from WP1 are consistent with animal results obtained from WP4 to show an increase of risk with cumulative exposure protracted at low exposure rate. At low cumulative exposures, no exposure rate effect is observed among miners, and in animals (CEA rats) the excess relative risk per WLM increases with exposure rate. Animal data are also consistent with previous studies of underground uranium miners showing an inverse dose rate effect at high cumulative exposures, but this effect disappears at low cumulative exposures.

Application of mechanistic models to both human and animal data allows to compare estimates obtained for the different stages of carcinogenesis. On animal data, the results of the different teams agree to show a much larger impact of radon on the first mutational step (initiation) rather than on the second mutational step (transformation) in the process of carcinogenesis. For human data, this statement is still valid, but GSF found a strong promotion effect of radon, and the effect of radon on initiation was only marginally significant in the French and in the Colorado miners cohort.

Cumulated risk estimates have been calculated among miners for specific scenarios (see table WP6.1). CEAR at 70 years ranges from 0 to 33 %, depending on the scenario (S1 to S8), model (BEIR VI models and preferred models from WP1 and WP5) and background rate (Czech or French miners). Among animals experiments performed in WP4, Lifetime Excess Absolute Risk (LEAR) vary from 0 to 20 % (see table WP4.1). When dividing by the corresponding cumulative exposure, excess absolute risk estimates vary from 1 to 24 10^{-4} per WLM in miners scenarios, and from 0 to 6 10^{-4} per WLM in animal experiments.

The combination of both approaches – epidemiology and animal experiments – in the same project permits to take advantage from both sources of data. Even if they can't support a direct estimation of the risk associated with radon exposure among human populations, the results obtained from animal

data are useful in bringing support to the results obtained among miners. Parallel application of mechanistic models to both human and animal data allows to derive hypotheses on the effect of radon on the different stages of carcinogenesis. Nevertheless, to go further in the comparison of risk estimates between human and animal data, additional work is needed, especially for rescaling the effect of age and the differences in organ dose [Hofmann 1993].

ESTIMATION OF RISK AMONG THE GENERAL POPULATION

One of the main aims of the project was to constitute a large data set at low levels of exposure, protracted over a long duration. WP1 provides risk estimates from a joint cohort of more than 10 000 Czech and French miners, with radon cumulative exposures lower than 1000 WLM (85% are below 100 WLM) received over a mean duration of more than 10 years. The degree of extrapolation for risk prediction among the general population is therefore reduced, in comparison to previous analyses of miners data (fig WP6.5). If we consider the correspondence:

1 WLM-mine == 1 year to an indoor concentration at 230 Bq/m^3, [ICRP 65, 1993]

then a cumulative exposure of 37 WLM in mines (which is the average of the cumulative exposure among the French cohort) is equivalent to 37 years of residency in a house with a concentration of 230 Bq/m^3 or 70 years at a concentration of 120 Bq/m^3 (which is approximately twice the average indoor radon concentration in France).

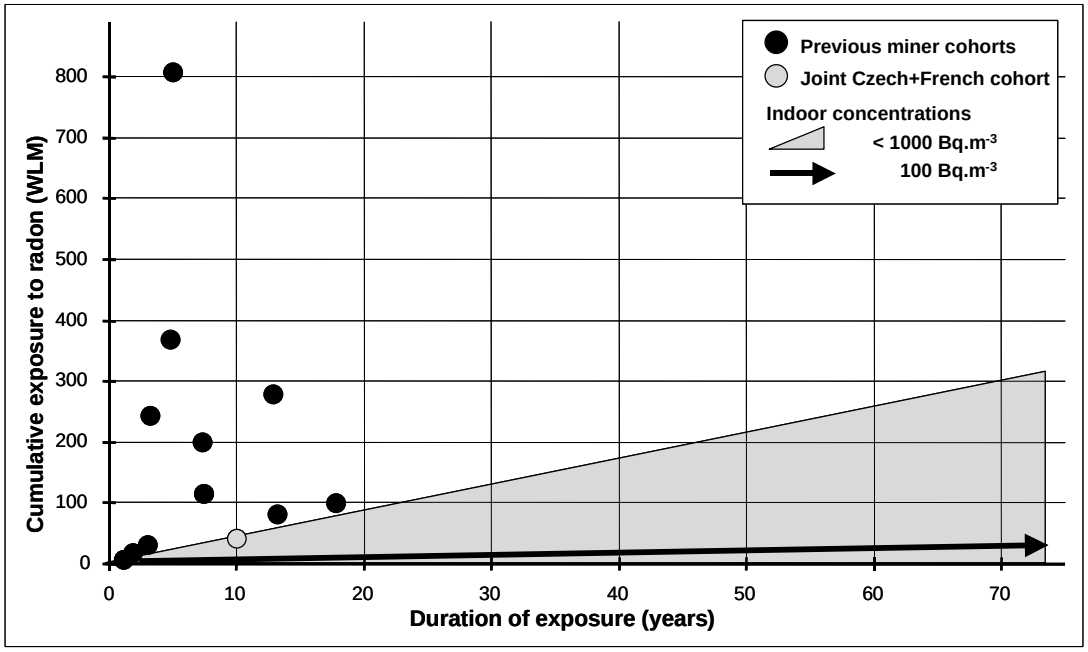

Fig. WP6.5: Schematic representation of the distance of extrapolation between miners cohorts and the general population. Previous miner cohorts: derived from [Lubin 1994]

The different model solutions proposed in the frame of the project can be used to extrapolate the risk from miners studies to residential exposures. As already underlined by previous works [BEIR VI 1999, Lubin 1997], such extrapolation necessitate several assumptions:

- The exposure-response relationship has a linear shape and can be extrapolated to low exposure rates observed in residential exposures,
- The estimated ERR per WLM can be transposed to females and to age ranges not included in miner populations,
- No modification is required to take into account the dosimetry of radon progeny in the lung,
- The ratio of ERR to exposure does not depend on other differences between miners and the general population (other pollutants present in the mines, smoking behaviour…).

Regarding the first point, the short distance of extrapolation for rates of exposure between the miner population included in our joint project and indoor exposures makes this first assumption more reliable than in previous works. Regarding the extrapolation outside the age range covered by miners studies, we recommend to fix the parameter reflecting the modifying effect of age at exposure when estimating risk associated with exposures during childhood.

The model derived from the joint analysis of Czech and French miners in WP1 and the models proposed in WP5 have been used to estimate the risk of lung cancer death attributable to indoor radon exposure. Several scenarios have been considered, with lifetime exposure to specific constant concentration of radon gas. These scenarios are the same as those considered in the BEIR VI report [BEIR VI 1999, table 3.5, p87]. The WP1 preferred model supposes that the exposure-risk relationship depends on age at median exposure. As no data are available at young ages from the French and Czech cohorts of miners, this modifying factor is fixed to a constant value below age 15. CERR at 70 years has been estimated for each "indoor scenario". Results are presented in table WP6.2.

Table WP6.2: Cumulated Excess Relative Risk of lung cancer death at 70 years calculated for several "indoor scenarios" using different risk models.

	Exposure				CERR at 70 years									
	age	rate	rate	cumul	BEIR 6 con		BEIR 6 dur		WP1 model		WP5 GSF		WP5 RIVM	
Scenario	(y)	($Bq.m^{-3}/y$)	(WLM/y)	(WLM)	Cz	Fr	Cz	Fr	Cz	Fr	Cz	Fr	Cz	Fr
S9	0 69	25	0.10	7.0	0.15	0.15	0.09	0.09	0.12	0.12	0.09	0.12	0.10	0.10
S10	0 69	50	0.19	13.3	0.28	0.28	0.18	0.18	0.22	0.23	0.17	0.23	0.20	0.20
S11	0 69	100	0.39	27.3	0.57	0.58	0.36	0.37	0.45	0.48	0.36	0.50	0.41	0.41
S12	0 69	150	0.58	40.6	0.85	0.87	0.53	0.55	0.67	0.71	0.56	0.76	0.63	0.63
S13	0 69	200	0.78	54.6	1.14	1.17	0.72	0.74	0.91	0.96	0.77	1.05	0.85	0.85
S14	0 69	400	1.56	109.2	2.28	2.34	1.44	1.48	1.81	1.92	1.65	2.22	1.81	1.81
S15	0 69	800	3.12	218.0	4.55	4.67	2.88	2.96	3.63	3.84	3.41	4.49	4.05	4.05

BEIR 6 con: BEIR VI "concentration-age-time since exposure" model as published in [BEIR VI 1999] ; BEIR 6 dur: BEIR VI "duration-age-time since exposure" model as published in [BEIR VI 1999] ; WP1 model: preferred model from the joint Czech and French analysis (see WP1, model M4), with coefficient for measured exposure and coefficient associated with age at median exposure fixed for age below 15 years ; WP5 GSF & WP5 RIVM: models retained by GSF and RIVM, as described in WP5 ; Cz : calculated using Czech national rates for background lung cancer mortality; Fr : calculated using French national rates for background lung cancer mortality

The values of CERR at 70 years are very similar between the different models. Almost no difference appears between estimates based on Czech or French background rates. The results are coherent with those obtained when applying the BEIR VI models.

To allow comparison with the values published in the BEIR VI report, the Lifetime Excess Relative Risk (LERR) has also been estimated. LERR values are calculated as the cumulated risk of lung cancer death up to age 110 years, while mortality by other causes is also taken into account. Table WP6.3 compares the estimated LERR by the WP1 preferred model with the results published in the BEIR VI report [BEIR VI 1999, table 3.5, p87].

Table WP6.3: Comparison of Lifetime Excess Relative Risk of lung cancer death at 110 years estimated for several "indoor scenarios" between the BEIR VI report and the model proposed by WP1.

	Exposure				LERR					
	age	rate	rate	cumul	BEIR 6 con		BEIR 6 dur		WP1 model	
Scenario	(y)	($Bq.m^{-3}/y$)	(WLM/y)	(WLM)	Smok+	Smok-	Smok+	Smok-	Cz	Fr
S9	0 99	25	0.10	10	0.09	0.10	0.06	0.07	0.08	0.08
S10	0 99	50	0.19	19	0.18	0.19	0.12	0.13	0.16	0.15
S11	0 99	100	0.39	39	0.35	0.39	0.24	0.26	0.32	0.31
S12	0 99	150	0.58	58	0.52	0.58	0.35	0.39	0.47	0.46
S13	0 99	200	0.78	78	0.68	0.77	0.46	0.52	0.63	0.61
S14	0 99	400	1.56	156	1.29	1.54	0.89	1.03	1.23	1.19
S15	0 99	800	3.12	312	2.30	3.06	1.65	2.05	2.31	2.27

BEIR 6 con and BEIR 6 dur: values as published in [BEIR VI 1999, table 3.5], males, Smok+: ever-smokers, Smok-: never-smokers ; WP1 model: LERR calculated at 110 years, using the preferred model from the joint Czech and French analysis (see WP1, table WP1.8, model M4), with coefficient for measured exposure and coefficient associated with age at median exposure fixed for age below 15 years ; Cz : calculated using Czech national rates for background lung cancer and all causes mortality; Fr : calculated using French national rates for background lung cancer and all causes mortality

The LERR estimated by the WP1 preferred model ranges from 0.08 to 2.31 according to the scenario. The choice of the background rate has almost no effect on the estimated LERR. The results lie between the estimates from the BEIR VI "exposure-age-concentration" and the "exposure-age-duration" models. The results from the WP1 preferred model are coherent with those published in the BEIR VI Report.

The estimation of risk in a general population has also been tested by RIVM. Using a previous TMC model derived from analysis of lung cancers induced by smoking and radon exposure in the Colorado miner cohort [Leenhouts 1999], the numbers of lung cancers in the Netherlands and Sweden attributable to smoking and radon were calculated. This analysis has been published in a scientific paper [Leenhouts 2001]. In the present project, the solution proposed by RIVM considers a uniform description of the effect of radon for the both the French and Czech cohorts of miners with distinctly different baseline lung cancer risks. It suggests the possibility of using the model for risk transfer across populations.

CONCLUSION AND PERSPECTIVES

RESULTS OBTAINED

The collaborative project "UMINERS + ANIMAL DATA" conducted within the 5th Framework Programme of the European Community provided new results in three different directions:

- Production of new data (for both humans and animals), with an increased statistical power to analyse the effect of radon at low cumulative exposure and low exposure rates,
- Better quantification of the relationship between radon exposure and the risk of lung cancer death, taking into account the potential modifiers of this relationship,
- Production of new knowledge on the effects of radon exposure at low exposure rate and low cumulative exposure, through the parallel analysis of animal and human data, and through the modelling of carcinogenesis mechanisms.

The project allowed the constitution of three cohorts of miners with low levels and long duration of exposure to radon, in France, Czech Republic and Germany. Together, the three cohorts constitute a set of more than 27 000 miners, with a detailed follow-up of annual individual exposures. Also four case-control studies have been developed within these cohorts, including a total of more than 1600 cases and 3600 controls. Reconstruction of cumulative exposure to radon and past consumption of tobacco is being completed. The project also allowed the finalisation of data from experiments that were initiated during the Fourth Framework Programme. In total, more than 4000 rats (plus 1500 non-exposed control rats) exposed to various exposure rates under controlled conditions have been followed-up over their whole life span. These data could serve as a basis for further research on the risks associated with radon, and more generally for alpha radiation. The animal databases will be transmitted to the European Radiobiology Archive and made available to other researchers interested in the field.

These data provided the necessary critical size to perform a detailed analysis of risk and to quantify the relationship between radon exposure and the risk of lung cancer. Together, the Czech and French miners cohorts comprise more than 10 000 individuals, with a mean duration of follow-up of more than 24 years. The total number of lung cancer deaths is 574. The joint analysis of these data confirms the existence of an increased risk of lung cancer death, associated with cumulative radon exposure. The excess relative risk per WLM decreases with increasing time since exposure and with increasing age at exposure. Application of mechanistic modelling on the same data showed a good agreement in the estimated risks. These results are coherent with the results of previous analyses performed on populations with higher levels of exposure.

Since the 1990's, a controversy persisted about the existence of an inverse exposure rate effect on the relationship between radon exposure and lung cancer risk. The evidence relied on both animal data and epidemiological results based on high levels of exposure to radon. Our project allowed the parallel analysis of data from rat experiments and from miners cohorts exposed to low cumulative exposures and low exposure rates. Animal and human data are concordant: no effect of exposure rate is observed at low levels of exposure. The analysis of data from the French and Czech miners show no exposure rate effect, but the possibility of an inverse dose rate effect cannot be excluded for exposure rates higher than 30 WLM/year. Similarly, the analysis of recent rat experiments indicates that at low cumulative exposures of about 100 WLM, the risk per WLM increases with exposure rate, but at high cumulative exposures, an inverse dose rate effect is observed. These data suggest that the induction of lung cancer is the result of a complex interplay between cumulative exposure and exposure rate. The application of multistage modelling to both animal and human data allowed investigating the role of radiation in the mechanism of carcinogenesis. On animal data, the results agree to show a much larger impact of radon on the first mutational step (initiation) rather than on the second mutational step (transformation) in the process of carcinogenesis. For human data, this statement is still valid, but a strong effect of radon on promotion is also possible.

DISSEMINATION AND USE OF THE RESULTS

The projects deliverables have been widely disseminated through the scientific literature, essentially through reports, communications and articles published in international scientific journals. At the date of end of the contract, the project led to more than 50 scientific communications or publications. Twenty-five additional publications or communications to scientific congresses are in preparation or scheduled over the next two years.

The users of the results are epidemiologists, health economists and researchers interested in the evaluation of the effects of radon on lung cancer risk; radiation protection officials wishing to examine the implications regarding protection from radon; individuals with an enhanced exposure to natural radiation in the home or at work; and public health officials responsible for programmes to reduce lung cancer death rates.

PERSPECTIVES

Many perspectives are opened by the work performed under this project. They could be direct extensions of the present project, or may constitute routes of further research toward a better knowledge of the risk linked to alpha exposure to low exposure rates. Other perspectives may be directed to the assistance in radiation protection and in formulating advice on cancer prevention.

The cohorts developed under WP1 will allow further analyses of the risk of cancer associated with radon exposure. The mean age at end of the follow-up is 56 and 55 years old respectively in the Czech and French miners cohorts. The follow-up of the French cohort has been recently extended up to 1999, but the detailed data analysis has yet to be performed. The continuation of the follow-up in the future will improve the coverage of the life span risk of death, and will allow a better determination of the time dependency of the dose-response relationship. The joint analysis of the French, Czech and German cohorts will increase the statistical power and the ability to detect even small variations of risk. From the French and Czech cohorts (but not the German cohort), an elevated risk of leukaemia seems to appear. Further analyses, possibly through nested case-control studies, might be worthwhile to investigate this observation. Also, the risk of other pathologies, including non-cancer causes, will be analysed. The work performed in the recent years has allowed the collection of data on other exposures (external gamma radiation, long live ore dust, diesel exhaust, arsenic, indoor radon concentration) and other risk factors (tobacco consumption, silicosis). These data will allow a multifactorial analysis of risk, and will permit to consider both the internal and external component of radiation exposure. The calculation of lung dose will provide a combined estimate of radiation exposure.

The case-control studies developed in the frame of WP2 and WP3 will allow further analysis of the interaction between radon and smoking. Data are in the process of being completed for the Czech study. Data for the French case-control study should be ready next year. Data collection has been completed in the German studies, and an updated job exposure matrix should be available soon. These data will also allow the consideration of indoor radon exposure and of an history of silicosis. The statistical analysis will be performed as soon as the data will be completed. The feasibility of a joint analysis of the data will be evaluated.

The processing of the data from animal experiments has been completed in the frame of WP4. The database constituted during the project has been transmitted to the European Radiobiology Archive. A joint analysis of both AEA-Technology and CEA data is in preparation for publication. Further statistical analyses of these data, especially for modelling the exposure-risk relationship, could be envisaged.

Mechanistic modelling of both human and animal data performed in the frame of WP5 will be continued in the future. Further research may be worthwhile to compare epidemiological and mechanistic approaches, and to derive some procedures to extrapolate the risk estimated from miners data to other populations. Furthermore, it was not possible to consider data on smoking in the frame of the present project. Further collaboration is needed to allow the transfer of data from WP2 to WP5,

and to allow the application of multistage models to analyse the combined effect of radon and tobacco on the risk of lung cancer death among miners.

The synthesis of the results performed in the frame of WP6 could be developed. Smoking will be considered, as soon as the results from the case-control studies will be ready. More elements are needed to allow a closer comparison of animal and human data. Some additional work should be made on the calculation of organ dose, considering combined sources of exposure. It may also be worthwhile to develop the work done on the calculation of lifetime risk estimates, and to complete the assessment of the different models in order to extrapolate the risk from miners data to the general population. A comparison of the results with those from the European project on indoor radon studies should also be performed in order to synthesise all the available knowledge on the effects of radon exposure.

CONCLUSION

The project involved three different fields of research: epidemiology, animal experiments, and mechanistic modelling. The collaboration allowed the exchange of data between the different partners, and also permitted some fruitful discussion between researchers of different background and an internal critical assessment of the data quality and of the results. This tight collaboration was a necessary basis to succeed in a synthesis of the results obtained from both human and animal data. Such a collaboration using multiple expertises may be continued in the future, and may be extended to many other fields of research.

The project had led to improved knowledge of the health effects of radon inhalation, and provides more information about factors that modify the associated lung cancer risk. The synthesis of the results of both human and animal data represents the state-of-the-art on the effect of radon at low dose and low exposure rate. This in turn could assist in the management of radon exposures and in formulating advice on lung cancer prevention. As a consequence, there should be a net benefit to health.

Miners cohorts provide information on a large population (several tens of thousand of individuals), with a good quality of follow-up (low percentages lost to follow-up) over a long duration (more than 24 years), and precise estimates of individual exposures. These data constitute a very good model to quantify the risks associated with chronic exposures to low rate of radiation. The size of the datasets, the long term follow-up and the good quality of the data assure the capacity to detect low risks, and to determine the potential impact of effect modifiers. The long term follow-up will allow to analyse the potential risks for non cancer causes of death. Furthermore, the work performed in the recent years has allowed the collection of data on other exposures (external gamma radiation, long-lived radionuclides in ore, diesel exhaust, arsenic, indoor radon concentration) and other risk factors (tobacco consumption, silicosis). These data will enable a multifactorial risk analysis. It will also permit to consider both the internal and external component of radiation exposure.

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