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# Risk of fatal versus incidental lung cancer in radon-exposed rats: A reanalysis of French data

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*This review summarizes data on lung cancer risk from radon experimental studies performed by our group in France with emphasis on the most recent findings and analyses on the influence of dose-rate and that of fatal versus incidental tumors. A dose-effect relationship was established in rats, which was very similar for medium and high cumulative exposures, to that observed in uranium miners. At low cumulative exposures in the range of 0.18 Jhm$^{-3}$ (50 WLM) to 0.36 Jhm$^{-3}$ (100 WLM), the proportion of fatal lung cancer is about 80% that of total lung cancers. In contrast, at cumulative exposures of 0.72 Jhm$^{-3}$ (200 WLM) and higher, the proportion of fatal lung cancer is about half that of total lung cancers. The parameters that influence fatal lung cancer risk are cumulative exposure, potential alpha energy concentration (PAEC), exposure rate, and protraction of exposure. At high cumulative exposures up to 10.8 Jhm$^{-3}$ (3,000 WLM), an inverse dose-rate effect similar to that observed in uranium miners was also found in rats. The inverse exposure-rate effect was observed mainly at the highest exposure-rates. In contrast, our recent results indicate that at relatively low cumulative exposures of 0.36 Jhm$^{-3}$ (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. These data suggest that the induction of lung cancer results from a complex interplay between cumulative exposure and exposure rate, with an optimal combination of these two parameters that results in a maximum risk of lung cancer induction. 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 those of underground uranium miners showing an inverse dose-rate effect at high cumulative exposures, but an attenuation of this effect at cumulative exposures lower than 0.18 Jhm$^{-3}$ (50 WLM). They support both an inverse dose-rate effect at high cumulative exposures, as well as its attenuation or disappearance at low cumulative exposures.*

**KEY WORDS:** *Lung Neoplasms; Risk Factors; Dose-Response Relationship, Radiation; Radon, Rats; Environmental Exposure*

## INTRODUCTION

Experimental animal studies were used in addition to epidemiological studies to investigate the effects of exposure, exposure rate, and other factors in predicting risks resulting from human radon exposures. This review summarizes data on lung cancer risk from radon experimental studies performed by our group at CEA-COGEMA (France) with emphasis on the most recent findings and analyses on the influence of dose-rate and that of fatal versus incidental induced lung cancers.

Experimental animal studies of radon-induced lung cancer are particularly helpful for understanding the carcinogenicity of human exposures both in the home and in the workplace. Animals can be exposed to a variety of agents under carefully controlled conditions and then sacrificed for the study of developing lesions or held for their lifespan for the development of tumors. Despite the fact that significant cumulative exposures at typical residential exposure rates of about 18 10$^{-3}$ Jhm$^{-3}$ (0.001 WLM per day) cannot be tested in a short-lived species like the rat, the rat model is valuable for confirming the conclusions acquired from human data particularly in regard to the exposure-rate effect. Radon health effect data, developed primarily in adult male rats were provided by the Pacific Northwest National Laboratory (PNNL) (1),

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formerly PNL, in USA, and in Europe by AEA-Technology in UK (2), and CEA-COGEMA in France (3). Under the Fourth Commission of the European Community Research and Development Framework Research Programme (4th CEC FP), a new series of experiments were carried out to investigate specifically the influence of exposure rate on lung cancer induction in rats. The animal experiments were conducted concomitantly at CEA (France) and AEA-Technology (Harwell, UK). They were performed at relatively low cumulative exposure comparable to lifetime exposures in high-radon houses or current underground mining exposures of around 0.36 Jhm$^{-3}$ (100 WLM). 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 (male Sprague-Dawley rats, 3-months old at the beginning of exposure). In addition, the metrology of the radon exposure atmospheres and the reporting of pathology were standardized between the two groups (4). 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. The results of the French experiments have been published recently (5). A paper reporting the results from AEA-Technology is in preparation. A joint analysis of both AEA-Technology and CEA-COGEMA rat data is also expected soon.

## FATAL AND INCIDENTAL LUNG TUMORS

Different analyses of various animal data sets have already been performed and the importance of categorization of lung tumors as fatal or incidental to the death of the animals was extensively discussed. The experiments conducted at CEA and AEAT were lifespan studies in which, after exposure, rats were kept and regularly observed until death and killed when moribund. Rats do not, generally, die from lung cancer. Thus, so-called fatal tumors that are thought to grow faster and to cause more serious health effects than incidental tumors were determined on the basis of histopathological criteria. Also close similarities exist between fatal tumors in rats and human lung cancers. An analysis of fatal and incidental lung tumours was performed in rats from the CEA-COGEMA data sets for which sufficiently detailed information was available and a full analysis of fatal tumors has been performed. In this analysis, a tumor was considered as fatal if one of the following criteria was satisfied (6): presence of a single metastasis or multiple metastases, tumor size depending on the structure affected, but generally larger than 15 mm in diameter, presence of marked necrosis affecting more than 50% of the lesion, extensive invasion into pleura, bronchi and/or blood vessels.

These assessment criteria have been found to be comparable with that used for PNNL rodent and dog data.

**Table 1.** Characteristics of exposures in the different experimental groups of rats exposed to radon and its progeny

| Exposure groups | Cumulative exposure | | PAEC | | Exposure rate | | Exposure duration |
|---|---|---|---|---|---|---|---|
| | [Jhm$^{-3}$] | WLM | [mJm$^{-3}$] | WL | [mJhm$^{-3}$d$^{-1}$] | WLM/day | *(days)* |
| Controls | 0.0009 | 0.25 | 0.0004 | 0.002 | 0.0003 | 0.0007 | Lifetime |
| Rn25LDR | 0.09 | 25 | 0.42 | 2 | 0.18 | 0.05 | 500 |
| Rn25HDR | 0.09 | 25 | 2.08 | 100 | 0.9 | 0.25 | 100 |
| RnD6 | 0.151 | 42 | 0.37 | 18 | 0.86 | 0.24 | 175 |
| Rn50HDR | 0.18 | 50 | 2.08 | 100 | 0.9 | 0.25 | 200 |
| RnD1 | 0.378 | 105 | 3.91 | 188 | 12.6 | 3.5 | 30 |
| RnPr | 0.385 | 107 | 3.06 | 147 | 4.64 | 1.29 | 83 |
| RnD3 | 0.361 | 100 | 1.21 | 58 | 4.01 | 1.11 | 90 |
| RnD12 | 0.36 | 100 | 1.85 | 13 | 0.95 | 0.26 | 375 |
| Rn200 | 0.72 | 200 | 24.96 | 1 200 | 18 | 5.0 | 40 |
| Rn500 | 1.80 | 500 | 24.96 | 1 200 | 36 | 10.0 | 50 |
| Rn1000 | 3. 6 | 1 000 | 24.96 | 1 200 | 72 | 20.0 | 50 |
| Rn3000 | 10.8 | 3 000 | 24.96 | 1 200 | 120 | 33.33 | 90 |
| Rn6000 | 21.6 | 6 000 | 24.96 | 1 200 | 120 | 33.33 | 180 |

**Table 2.** Number and proportion of total and fatal lung cancers in the different experimental groups of rats exposed to radon and its progeny

| Exposure groups | Number of rats at risk | Total number of lung cancers | Total proportion of lung cancers | Number of fatal lung cancers | Proportion of fatal lung cancers | Lifetime Excess Absolute Risk (%) |
|---|---|---|---|---|---|---|
| Controls | 1521 | 6 | 0.39 | 1 | 0.07 | 0 |
| Rn25LDR | 497 | 3 | 0.60 | 1 | 0.20 | 0.14 |
| Rn25HDR | 496 | 11 | 2.22 | 2 | 0.40 | 0.34 |
| RnD6 | 211 | 3 | 1.42 | 2 | 0.95 | 0.88 |
| Rn50HDR | 497 | 19 | 3.82 | 13 | 2.62 | 2.55 |
| RnD1 | 240 | 17 | 7.08 | 14 | 5.83 | 5.77 |
| RnPr | 240 | 7 | 2.92 | 4 | 1.67 | 1.60 |
| RnD3 | 240 | 10 | 4.17 | 5 | 2.08 | 2.02 |
| RnD12 | 240 | 12 | 5.0 | 8 | 3.33 | 3.27 |
| Rn200 | 199 | 28 | 14.07 | 8 | 4.02 | 3.95 |
| Rn500 | 99 | 30 | 30.3 | 16 | 16.16 | 16.09 |
| Rn1000 | 100 | 35 | 35.0 | 15 | 15.0 | 14.93 |
| Rn3000 | 50 | 20 | 40.0 | 10 | 20.0 | 19.93 |
| Rn6000 | 50 | 8 | 16.0 | 2 | 4.0 | 3.93 |

Table 1 summarizes the characteristics of exposure in the different experimental groups of rats exposed to radon and its progeny. Table 2 summarizes the number and proportion of total lung cancers as well as that of fatal lung cancers, as classified by the system defined above. In this analysis, control rats from both AEA-Technology and CEA-COGEMA were pooled together (same strain, sex, age at exposure...). In the CEA-COGEMA studies, five cases of lung cancers were observed in a series of historical controls, but none of them could be considered as fatal. In a series of 240 control rats, contemporary of the last dose-rate effect study (5), no lung tumor was observed. So, there was no fatal lung cancer among the 1025 control rats from our data sets. In contrast, one case of fatal lung cancer was observed among the AEA-Technology 496 control rats. Thus, it was agreed between both institutes to pool their control rat data sets, allowing us to establish the background incidence of fatal lung cancers in controls at 1 in 1521 rats (0.07 %).

## DOSE-EFFECT RELATIONSHIP

It has been demonstrated that exposure to radon and its progeny induces lung cancer in rats (7). An excess risk of lung cancers was observed in rats at cumulative exposure as low as 0.09 Jhm$^{-3}$ (25

WLM) performed at relatively high potential alpha energy concentration (PAEC) of about 2.1 mJm$^{-3}$ (100 WL) (8). A dose-effect relationship was established showing that the incidence of lung cancers in rats exposed to radon/radon progeny increased with cumulative exposure (3). Figure 1 shows the incidence of total and fatal lung cancers in rats exposed at cumulative exposures up to 21.6 Jhm$^{-3}$ (6,000 WLM). The proportion of both total and fatal lung cancers in rats increased for cumulative exposures ranging from 0.09 Jhm$^{-3}$ (25 WLM) up to 10.8 Jhm$^{-3}$ (3,000 WLM), and decreased thereafter. However, in rats that received at cumulative exposure of 0.72 Jhm$^{-3}$ (200 WLM) or higher, the proportion of fatal lung cancer is about half that of total lung cancers.

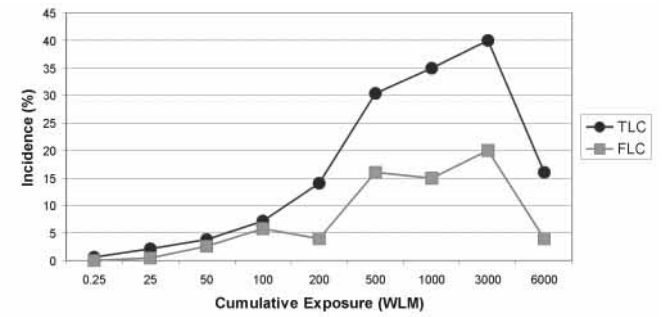


**Figure 1.** Compared incidence of total (TLC) and fatal (FLC) lung cancers in rats exposed to radon and its progeny at various cumulative exposures (0.25 WLM is the estimated cumulative exposure of controls)

For medium and high cumulative exposures, the pattern of this dose-effect relationship was very similar to that observed in underground uranium miners in whom a significant excess of lung cancers was observed for cumulative exposure ranging from about 0.36 Jhm$^{-3}$ (100 WLM) to 1.44 Jhm$^{-3}$ (400 WLM) and above (9). However, excess respiratory tract tumors were produced in rats at exposures considerably lower than 0.36 Jhm$^{-3}$ (100 WLM), even at cumulative exposures (although not exposure rates) comparable to typical lifespan exposures in homes at about 0.09 Jhm$^{-3}$ (25 WLM).

A cumulative exposure of 0.09 Jhm$^{-3}$ (25 WLM), at a high exposure rate of 2.08 mJm$^{-3}$ (100 WL), resulted in a three to four-fold increased lung cancer frequency in male Sprague-Dawley rats as compared to unexposed control rats (10). At cumulative exposures of 0.18 Jhm$^{-3}$ (50 WLM) and 0.36 Jhm$^{-3}$ (100 WLM), the proportion of fatal lung cancer is about 80% that of total lung cancers. In the PNNL experiments, more than 70% of squamous cell (epidermoid) carcinomas, but only 20% of the adenocarcinomas were classified as fatal. Similar findings were also observed in our experiments but the situation was somewhat different in the different experimental groups according to the cumulative exposures and the PAEC at which the animals were exposed. In rats exposed at cumulative exposures of about 0.36 Jhm$^{-3}$ (100 WLM) and lower, the proportion of fatal squamous cell carcinomas (57%) and that of fatal adenocarcinomas (59%) was quite similar, and 3 on 4 of adenosquamous carcinomas (75%) should be considered as fatal.

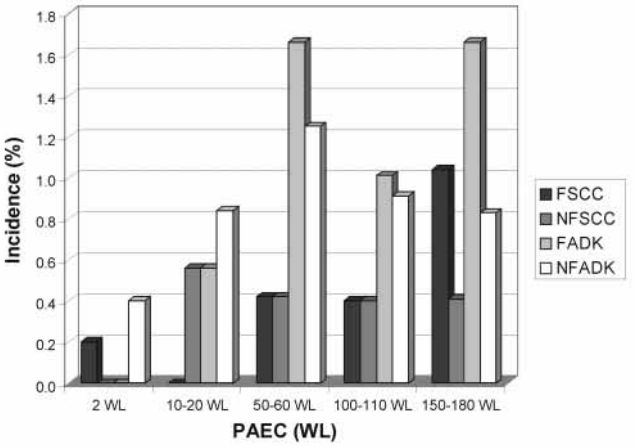


**Figure 2.** Relative proportion of fatal and non fatal lung cancers according to their histological types in rats exposed at 100 WLM and lower and various PAEC (FSCC: fatal squamous cell carcinoma; NFSCC: non fatal squamous cell carcinoma; FADK: fatal adenocarcinoma; NFADK: non fatal adenocarcinoma)

Figure 2 shows the relative incidence of squamous cell carcinomas and adenocarcinomas in rats exposed at 0.36 Jhm$^{-3}$ (100 WLM) and lower, according as a function of PAEC. Roughly, the frequency of fatal squamous cell carcinomas that are related to the severity of the aggression of the carcinogenic agent, increased with increasing PAEC.

In rats that received cumulative exposures of about 0.36 Jhm$^{-3}$ (100 WLM) or lower, the first observed death was due to a bronchoalveolar adenocarcinoma that occurred at the age of 589 days in a rat exposed at 0.18 Jhm$^{-3}$ (50 WLM) and high PAEC of 2.08 mJm$^{-3}$ (100 WL). However, except for one rat that died from a squamous cell carcinoma very late (1,019 days of age), the majority of squamous cell carcinoma deaths occurred very early in the lifetime of rats. The first two deaths from squamous cell carcinomas occurred at the age of 589 and 596 days in groups Rn50HDr and RnD1, respectively, and almost all of these deaths occurred before 900 days of age. In contrast, adenocarcinoma deaths occurred later, between 800 and 1100 days of age, and were evenly distributed over the last 300 days of rat lifetime.

Figure 3 shows the relative incidence of squamous cell carcinomas and adenocarcinomas in rats exposed at 0.7 Jhm$^{-3}$ (200 WLM) and higher, which were exposed at a similar PAEC of about 25 mJm$^{-3}$ (1,200 WL). Roughly, the frequency of fatal squamous cell carcinomas, increased with cumulative exposures up to 10.8 Jhm$^{-3}$ (3,000 WLM) and decreased thereafter.

In contrast, the frequency of fatal adenocarcinomas, increased with cumulative exposures only up to 1.8 Jhm$^{-3}$ (500 WLM) and decreased thereafter. In rats exposed at cumulative exposures of about 0.72 Jhm$^{-3}$ (200 WLM) and higher, the proportion of fatal

squamous cell carcinomas (66%) and that of fatal adenocarcinomas (30%) was quite similar to that observed in PNNL rats. On the other hand, 4 of the 6 observed adenosquamous carcinomas (66%) were considered fatal. It should be noted that PNNL used Wistar rats.

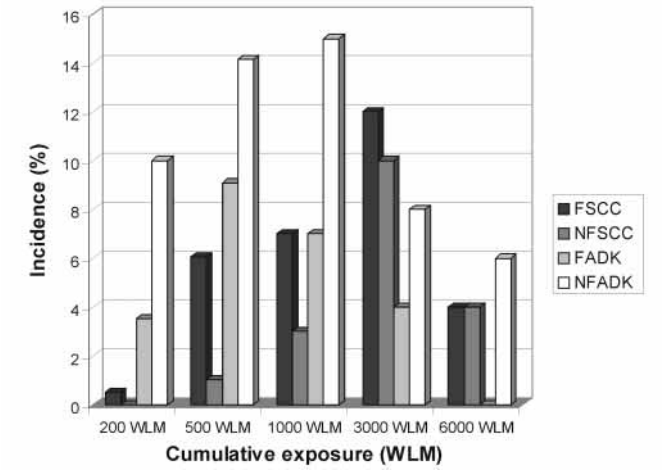


**Figure 3.** Relative proportion of fatal and non-fatal lung cancers according to their histological types in rats exposed at cumulative exposures of 200 WLM and higher and similar PAEC of 1,200 WL (FSCC: fatal squamous cell carcinoma; NFSCC: non fatal squamous cell carcinoma; FADK: fatal adenocarcinoma; NFADK: non fatal adenocarcinoma)

In rats exposed at cumulative exposures higher than 0.72 Jhm$^{-3}$ (200 WLM), the first lung cancers deaths were of the squamous cell type and occurred very early, at 365 days of age, in rats exposed at 1.8 Jhm$^{-3}$ (500 WLM) and a high PAEC of about 25 mJ m$^{-3}$ (1200 WL). About two-thirds of squamous cell carcinomas deaths occurred before 600 days of age. In contrast, adenocarcinomas deaths occurred later in life and were evenly distributed between 420 and 930 days in the rat lifetime. About 80 % of the adenocarcinomas observed in rats exposed at 0.72 Jhm$^{-3}$ (200 WLM) and higher were not fatal. These tumors were generally small in size, poorly invasive and they did not metastasize. They occurred very late in the lifetime of the animals or, in other words, they allow the rats to live with their lung cancer. This could explain why rats bearing lung tumors, whether fatal or not, live generally longer than those without lung tumors (11). These observations also suggest that the kinetics of development of incidental tumors and especially that of adenocarcinomas, including parameters like cell growth, doubling time, etc., would be different from that of squamous cell carcinoma and adenosquamous carcinomas and involve different cellular and molecular mechanisms.

## LIFETIME EXCESS ABSOLUTE RISK

Figure 4 shows the lifetime excess absolute risk (LEAR) of lung fatal cancers in rats exposed to radon and its progeny at various cumulative exposures and PAEC. The lifetime LEAR increases with cumulative exposures up to 10.8 Jhm$^{-3}$ (3,000 WLM), and decreased thereafter. The higher LEAR values are observed in groups exposed at high cumulative exposures of 0.36 Jhm$^{-3}$ (100 WLM) and higher and high PAEC of 3.91 mJ m$^{-3}$ and 25 mJm$^{-3}$ (188 WL and 1200 WL), respectively. In contrast the lowest LEAR values (≤ 5%) are observed in rats exposed at cumulative exposures lower than 0.36 Jhm$^{-3}$ (100 WLM) and PAEC lower than 2.08 mJm$^{-3}$ (100 WL).

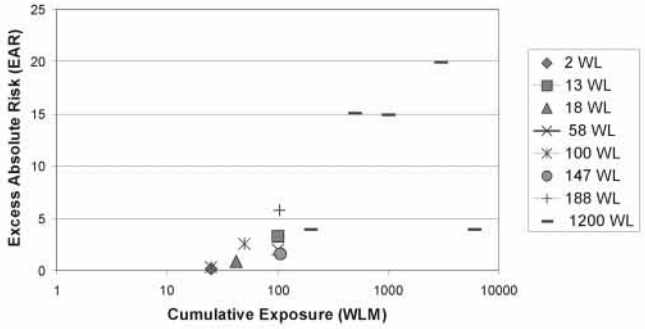


**Figure 4.** Lifetime excess absolute risk (x 10$^{-4}$) of fatal lung cancer in rats exposed at various cumulative exposures (WLM log transformed) and potential alpha energy concentrations (PAEC, expressed in WL)

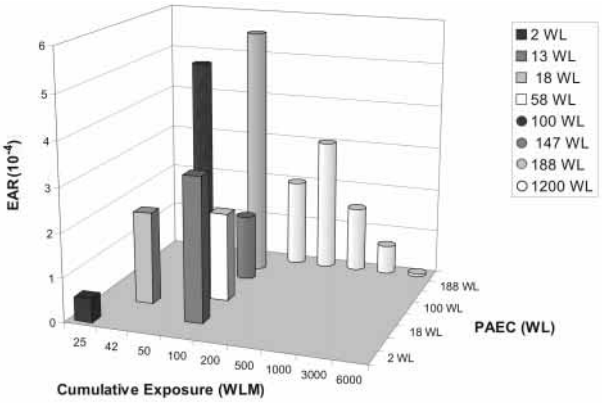


**Figure 5.** Schematic representation of the lifetime excess absolute risk (x 10$^{-4}$) per WLM of fatal lung cancer in rats exposed to radon and its progeny at various cumulative exposures (WLM) and PAEC (WL). Note that x (WLM) and y (WL) axes are categorical

Figure 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) of fatal lung cancers 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. The risk of lung tumor induction in rats appears to be maximal for cumulative exposures ranging from 50 WLM up to 100 WLM, and PAEC ranging from 58 WL up to 188 WL.

In the same way, Figure 6 shows the combined influence of

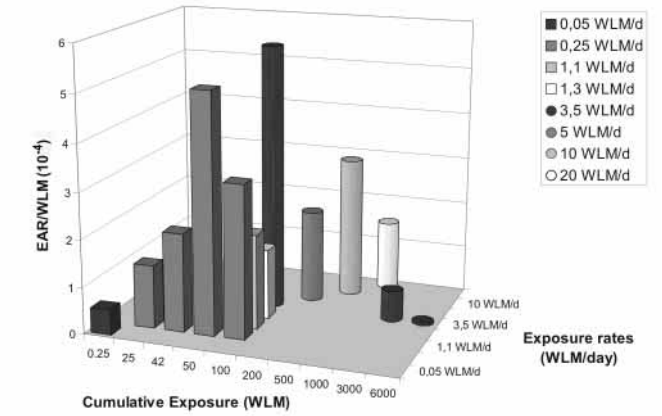


**Figure 6.** Schematic representation of the lifetime excess absolute risk (x $10^{-4}$) per WLM of fatal lung cancer in rats exposed to radon and its progeny various cumulative exposures (WLM) and exposure rates (WLM/day). Note that x (WLM) and y (WLM/day) axes are categorical

cumulative exposure expressed in terms of WLM and of exposure rate, expressed in terms of WLM per day, on the excess absolute risk per unit exposure (EAR per WLM) of fatal lung cancers 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 exposure rates. In contrast, for cumulative exposures lower than 100 WLM, the risk of lung cancer decreases with decreasing exposure rates. Moreover, the risk of lung tumor induction in rats appears to be maximal for cumulative exposures ranging from 50 WLM up to 107 WLM, and exposure rates ranging from 1.1 WLM per day up to 3.5 WLM per day.

## DISCUSSION

In the present study, an important effort has been made to discriminate incidental from fatal tumors and a full analysis of fatal tumors has been performed. One advantage of such animal data over human data is that they provide rigorous and detailed information and risk estimates over the whole life of the animals. The analysis of the data showed that the parameters that influence fatal lung cancer risk are cumulative exposure, PAEC, exposure-rate, and protraction of exposure. The highest fatal lung cancer risk is observed in rats exposed at about 0.36 Jhm$^{-3}$ (100 WLM), at high PAEC in the range of 3 to 4 mJm$^{-3}$ (150-200 WL), and/or high exposure-rate from about 3.5 to 5 WLM/day, delivered over a short period (30 days). At cumulative exposures lower than 0.18 Jhm$^{-3}$ (50 WLM), the risk decreases with decreasing PAEC, decreasing exposure rates and increased protraction of exposure. At cumulative exposures higher than 0.72 Jhm$^{-3}$ (200 WLM), the highest risk occurred in rats exposed at 1.8 Jhm$^{-3}$ (500 WLM), high PAEC of about 25 mJm$^{-3}$ (1,200 WL), and/or high exposure-rate of about 10 WLM/day, delivered for a short period of time of about 50 days. At very high cumulative exposures of about 1.8 Jhm$^{-3}$ (500 WLM) and higher, the risk decreases with increased cumulative exposure, decreasing exposure rates and increased protraction of exposure. The highest proportion of squamous cell carcinomas that is related with the severity of the aggression of the carcinogenic agent and thus the severity of the health detriment, was observed in rats exposed at high PAEC and decreased with decreasing PAEC. The larger and most invasive tumors were also observed in rats exposed at high PAEC and the size and invasiveness of tumors decreased with decreasing PAEC and/or increasing protraction of exposure.

This analysis confirms previous results, showing that at high cumulative exposures, the risk of lung cancers in rats increases with decreasing PAEC (5). This effect, which is also observed in underground miners, is called the inverse dose-rate effect or protraction enhancement effect. 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 PAEC, i.e., exposure-rate, confirming the results obtained at lower cumulative exposures (10). The inverse exposure-rate effect was observed mainly at the highest exposure-rates. The pattern of the diagrams showing the influence of cumulative exposure expressed in terms of WLM and of PAEC, expressed in terms of WL, or exposure rate expressed in terms of WLM/day, on the excess absolute risk per unit exposure (EAR per WLM) of fatal lung cancers in rats is very similar to that obtained when considering the influence of these parameters on the excess relative risk (ERR) per WLM of total lung cancers (11). The use of the excess absolute risk allows us to compare the number of additional fatal lung cancer cases in the different groups of rats by taking into account the absolute value of background incidence in controls. In the present analysis, the lifetime excess relative risks (LERR) per WLM ranged between 1 and 6%, and were higher than that estimated in human exposed populations, mainly underground miners. In contrast the LEAR of fatal lung cancer per WLM in our animal experiments, ranged between 0.06 and 5 $10^{-4}$, and were comparable with that estimated in miners studies.

These data suggest that the induction of fatal lung cancer is the result of a complex interplay between cumulative exposure and exposure rate, with an optimum combination of these two parameters that results in a maximum risk of tumor induction. 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 an attenuation of this effect at cumulative exposures lower than 50 WLM (12). In

that way, no dose-rate effect was observed in the recent joint analysis of Czech and French uranium miners exposed to low cumulative exposures (mean cumulative exposures of 36.5 WLM and 57.3 WLM, respectively) (13). Even if they cannot provide a direct estimation of the risk associated to radon exposure among human populations, the risk estimates obtained from animal data are useful because of their similarities with those obtained in underground miners. Our experimental data support both an inverse dose-rate effect at high cumulative exposures, as well as its attenuation or disappearance at low cumulative exposures. Quantitative modeling 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 as in various miner studies (14-16). During the Fifth CEC FP, a risk analysis of animal data was performed in connection with AEA-Technology and different partners involved in statistical modeling (13). This allowed comparison of the different data sets of recent animal data from partners of CEA and AEA-Technology on exposure rate with those of previously analyzed data, to scale biological parameters and risk between rats and humans and to achieve statistical modeling of the underlying mechanisms. Statistical modeling of animal data provided qualitative agreement with miners' solutions. Nevertheless, to go further in the comparison of risk estimates between human and animal data, additional effort is needed, especially for adapting the effect of age and the differences in organ dose (17).

### *Footnote*

*Radiological protection units. A working level (WL) is defined as any combination of the short-lived radon progeny in one liter of air, under ambient temperature and pressure, that results in the ultimate emission of 1.3 $10^5$ MeV of alpha particle energy. One WL corresponds approximately to the potential alpha energy concentration (PAEC) of short-lived radon decay products in air that are in equilibrium with a radon gas concentration of 3.7 $10^3$ Bq $m^{-3}$ of air (100 pCi $l^{-1}$ of air). The potential alpha energy exposure of miners is often expressed as working level months (WLM). This unit is generally used to estimate exposure to radon decay products in epidemiological studies of miners and for establishing radiation limits in mines. One WLM corresponds to exposure to a concentration of 1 WL for a reference period of 170 hours: 1 WLM = 170 WLh = 3.5 mJ h $m^{-3}$*

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