Carcinogenicity of radon/radon decay product inhalation in rats – effect of dose, dose rate and unattached fraction

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Abstract
Purpose: The effects of inhalation of radon/radon decay products at different total doses, dose rates and ‘unattached’ fractions were investigated in a life span study in rats.

Materials and methods: 1574 rats inhaled radon/radon decay products in a purpose-built recirculating exposure system that provided stable/reproducible exposure conditions. 501 were maintained as controls.

Results: Lung tumour incidences were significantly elevated in most exposed groups. The study power was insufficient to resolve the shape of the dose and dose rate response curves, but combination of this data with that from other studies demonstrated that for high cumulative exposures, the lifetime excess absolute risk increases with increasing exposure durations and for low cumulative exposures the opposite trend occurs. Exposure did not increase leukaemia incidences. A small number of non-lung tumour types including mammary fibroadenoma showed elevated incidences in some exposed groups, however not consistently across all exposure groups and showed no dose or dose rate relationship.

Conclusions: Radon/radon decay product exposure caused excess lung tumours in rats along with limited non-lung effects. The results are consistent with the findings that at low cumulative exposures decreasing exposure concentrations or protracting the time over which the dose is delivered, reduces lung tumour risk. At higher levels, decreasing exposure concentrations or protracting exposure time increases lung tumour risk.

Keywords: Radon, inhalation, rats, carcinogenicity, lung cancer

Introduction
Much of the evidence of the health effects of radon/radon decay product exposure originates from detailed epidemiological studies of uranium miners. However miner exposures were generally at relatively high levels and high exposure rates when compared with the domestic situation and exposure conditions in homes may be somewhat different to those encountered in mines. Assessment of the risk from domestic exposure therefore requires an understanding of the effect of these factors on risk.

In the late 1980s, a research programme was initiated by the UK Department of Health, at Harwell, to investigate the health effects of radon/ radon decay product exposure and exposure characteristics that modified the extent of these effects. The work was conducted in rats and the first phase was to construct a facility suitable for their exposure. This work complimented and augmented that done by groups in France (Commissariat L’Energy Atomique, CEA, France) and the USA (Pacific Northwest National Laboratory, PNNL, Batelle Laboratories, USA).

The facility has been described in detail in previous publications (Strong & Walsh 1990, Walsh & Strong 1990). It is described briefly here. To limit the extent of the release of radon decay products to atmosphere and to minimize the activity of the sources required for generation of the exposure aerosol, the system was designed as a sealed re-circulating unit. It consisted of a large stainless steel chamber (3m3) containing a rotating carousel carrying the animal cages. For each exposure approximately 50 rats were held in the
The radon/radon decay products were generated from an exponential series of 226Ra sources (0.5–8 × 10^5 Bq) any of which could be opened or closed to allow any predetermined concentration required to be achieved with a high degree of accuracy. In the domestic situation, radon decay products are attached to ambient aerosol. To represent this, the radon/radon decay products aerosol was mixed with a carnauba wax aerosol in a mixing chamber and then supplied to the chamber containing the animals. This allowed the radon decay products to become attached to an aerosol as they would in the domestic situation. The wax aerosol was 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). When wax aerosols were used, particle concentrations in the chamber were in the order of 8 × 10^5 cc^-1 and potential alpha energy ‘unattached’ fractions were less than 1.5%. To achieve exposures at high ‘unattached’ fractions (approximately 60%) radon/radon decay products were supplied to the animal chamber without aerosol present. As the system was sealed, conditioning of the air was necessary to remove excess water, carbon dioxide and ammonia and to replenish the oxygen levels before being returned to the exposure chamber via the mixing chamber. During all exposures radon decay product concentrations (218Po, 218Pb and 214Bi) in the chamber were measured hourly using a semi-continuous measuring system that also provided information on the ‘unattached’ fraction of these nuclides, particulate levels, and environmental conditions (Strong 1991). As exposures continued through the 1990s, the instrumentation was refined to provide automatic feedback to control the release of radon/radon decay products from the sources using electronically controlled valves. The facility was completed and commissioned in 1992. Exposures for the life span studies took place between October 1993 and May 1998.

A second chamber, identical to that described above in terms of air handling, wax generation and construction, but without the radon/radon decay product injection was used for control animal exposures. To achieve gamma dose rates to the animals (control and exposed) that were as low as possible and similar for both groups (<20 μSv hr^-1), the radon sources were held in shielded glove-boxes above the two chambers and were distributed such that the gamma dose rate received by the two exposure chambers was similar for both chambers.

Metrology intercomparisons involving the Harwell and CEA groups were conducted at both facilities so that measurements by both were comparable (Strong et al. 1994a, 1994b). Later studies investigated and compared methods of measuring deposition of radon decay products in the respiratory tract during animal exposures (Strong & Baker 1996, Strong et al. 1996).

Prior to the start of life span studies, preliminary investigations on the early effects of exposure were conducted in the facilities at CEA and at Harwell (Taya et al. 1992, Bisson et al. 1994). These investigated the use of biological markers of exposure to radon/radon decay products. Exposure to radon/radon decay products resulted in enhanced cell proliferation (measured by uptake of bromodeoxy-uridine BrdU) in the bronchial, bronchiolar and tracheal epithelium and increases in the incidences of alveolar macrophages demonstrating nuclear aberrations (binucleated and micronucleated cells). Both of these effects peaked 14 days after exposure and all further investigations of these markers were conducted 14 days after exposure (Collier et al. 1996). These markers of early damage were used to optimize the age of the animals used for the life span studies. It had been suggested that young animals appeared particularly sensitive to radon decay product exposure. Animals ranging in age from 3–40 weeks were exposed in the Harwell facility. Exposure at 440 Working Level Months (WLM) (equivalent to 5.7 kJ m^-3 s^-1) caused a doubling in epithelial cell proliferation in all age groups studied. However for young animals (<12 weeks old) baseline epithelial proliferation rates were up to 40 times higher than those of adults, so a doubling as a result of radon/radon decay product exposure had a very significant effect (Baker 1996, Collier et al. 1997). For this reason all life span studies at Harwell were conducted in animals older than 12 weeks at exposure.

The major goal of these studies was to extend the animal data on the effects of radon/radon progeny exposure to lower doses and dose rates than had been studied previously at CEA and PNNL. In order to do this a base line dose response at doses/dose rates comparable to those used by the other laboratories was required to ensure that results from this new facility were directly comparable. This objective was met in Study 1. The effect of dose rate was investigated in Study 2 and the effect of dose rate at lower doses was investigated in Study 3. Under a European Union Framework contract, the doses and average dose rates for these studies were chosen to be similar and complimentary to those being studied at the CEA, however the exposures conducted at the
CEA were undertaken over the course of a normal working day/week, whereas the exposures described in these studies were continuous 24 h a day, 7 days a week. Hence for a similar average daily exposure rate in studies conducted at CEA and under these studies, the CEA animals received a more fragmented dose (working hours only) at an instantaneous higher dose rate.

**Methods**

The methods have been detailed elsewhere (Collier et al. 1999, 2001). In summary, adult male Sprague Dawley rats (Harlan Olac, Oxon, UK) were exposed to radon/radon decay products in the Harwell facility as detailed above. Whilst most of the animals in any exposure group were kept for their life span, a small number of animals (usually 2 per exposure) were removed during the exposures to measure deposition of radon decay products. These were exposed for a minimum of four hours and then removed from the chamber and killed (intraperitoneal injection of sodium pentobarbitone, Sigma-Aldrich Ltd, Gillingham, Dorset, UK). The lungs were excised, weighed and the radon decay product concentration was determined by gamma spectrometry. After exposures were complete animals were housed and maintained normally for the remainder of their life span. A small number from each exposure group (approximately 2 animals) was taken 14 days after exposure to determine early effects of exposure (epithelial cell proliferation and macrophage aberration induction, methods have been given previously, Taya et al. 1992, Collier et al. 1996, 1997, 1999). Briefly these animals received 5-Bromo-2-deoxyUridine (BrdU 4 ml, 5 mg/ml i.p. Sigma-Aldrich, Gillingham, Dorset, UK). They were killed 4 h later (sodium pentobarbitone, Sigma-Aldrich, Gillingham, Dorset, UK given i.p.) followed by exsanguination via abdominal aorta. Bronchoalveolar lavage (5 × 5 ml sterile 0.15 M saline, Sigma-Aldrich, Gillingham, Dorset, UK) was used to recover free cells from the lungs. Total number of cells recovered was assessed using a Coulter counter (BeckmanCoulter, High Wycombe, Bucks, UK) and Cytospins were prepared and stained (May-Grunwald geimsa), from the lavage fluid. Differential cell counts on 500 cells/slide were performed on two slides from each animal and the number of binucleated and micronucleated alveolar macrophages was assessed. To assess epithelial cell proliferation, the lavaged lungs were inflated with fixative (1% acetic acid in 90% ethanol, Sigma-Aldrich, Gillingham, Dorset, UK), excised and stored in fixative at 4°C. The left lobe was embedded in paraffin wax and 5 serial 4 μm sections were taken. One was stained with haematoxylin and eosin (H&E), two for BrdU (biotin/avidin system, Vector Laboratories, Peterborough, Cambs, UK), and two controls for non-specific staining with BrdU (these followed the same procedure as for the BrdU slides but were not incubated with anti-BrdU). Incorporation of BrdU in a cell was expressed by the formation of black deposits in the cell nuclei. The slides were viewed at 40 ×. The total number of cells present per field was assessed in the H&E stained slides over approximately 20 fields per slide. The number of BrdU stained cells was assessed in the BrdU and control slides over 20 fields per slide. The net labelling index (LI) was calculated according to Equation 1.

\[
\text{LI} = \frac{\text{No. positive cells in 20 fields on BrdU slides} - \text{no. of stained cells in 20 fields in control slides}}{\text{Total number of cells in 20 fields from H&E slides}}
\]

Remaining animals were examined daily for signs of ill health and were either killed in extremis or found dead. At death the survival since birth and since exposure was calculated and a detailed necropsy examination was conducted. The lungs and all major organs were examined and findings recorded. The lungs, heads and spleens were routinely fixed, along with any abnormalities found at dissection. All non-lung samples were processed to wax, sectioned and stained with haematoxylin and eosin. In most cases, the lungs were partially dehydrated and stained (Wright’s). Dehydration was completed and the stain differentiated. The tissue was then rendered transparent using methyl salicylate (Sigma-Aldrich, Gillingham, Dorset, UK). All lungs were then examined under a dissecting microscope for the presence of tumours. These were seen as dark staining areas in the relatively clear tissue. This ‘clearing’ method allowed rapid detection of both peripheral and deep lung tumours greater than 1 mm in diameter. Any tumours detected were dissected and conventionally processed through wax for sectioning. Clearing of the lungs was not possible for animals that were found dead (17%) rather than killed. For these, the lungs were processed conventionally and step sections were taken at 2 mm steps through the whole lung to ensure that all...
tumours < 1 mm were highly likely to be detected. All samples were transferred to a pathologist for examination. All of the sections were read ‘blind’. All findings were diagnosed according to the EULEP (European Late Effects Project Group) pathology scheme (Bannasch & Gossner 1997).

The tumours diagnosed in the lung were classified according to the scheme given in Table I. If any of the following criteria were satisfied, a primary malignant lung tumour was classified as fatal (likely to lead to death) (Dagle et al. 1993):

- Presence of a single metastasis or multiple metastases;
- Tumour size depending on the structure affected, but generally > 15 mm dia.;
- Presence of marked necrosis affecting more than 50% of the lesion;
- Extensive invasion into pleura, bronchi and/or blood vessels.

These assessment criteria were originally defined by the CEA (Renaud & Merlier 1975) and have been found to be comparable with a similar index used for Batelle rodent and dog data (Monchaux personal communication).

Non-tumour lung histopathology and any histopathology found outside the lung was also recorded.

A database was constructed giving for each animal the total cumulative exposure in Working Level Months (WLM) and the average exposure concentration in Working Levels (WL), both as target and achieved values (from the online metrology), the dates of birth, exposure dates (start and end) and date of death, the reason for death, the diagnosis from histopathology of any lung tumours or non-tumour lung pathology, the classification of any lung tumours into fatal or non-fatal according to the criteria of the CEA and details of any non-lung histopathology/histology. This data has been passed to the EULEP radiobiology archive (Gerber et al. 1999) for use by other researchers in this field. Multiple lung tumours of the same type and multiple lung tumours of different types were observed in a few of the animals.

Three studies were conducted. In Study 1 groups of animals were exposed at a constant exposure concentration (approximately 1000 Working Levels, WL equivalent to 0.021 J m\(^{-3}\)) for varying lengths of time to give cumulative exposures in the range 200 – 3200 WLM (2.62 – 41.5 kJ m\(^{-3}\) s\(^{-1}\)). In Study 2, cumulative exposures of approximately 1000 WLM (13 kJ m\(^{-3}\) s\(^{-1}\)) were delivered at various exposure concentrations (250 – 2000 WL, 0.005 – 0.04 J m\(^{-3}\)). In Study 3, the effect of low cumulative doses (approximately 100 WLM, 1.3 kJ m\(^{-3}\) s\(^{-1}\)) delivered at a range of dose rates (15 – 900 WL, 0.0003 – 0.019 J m\(^{-3}\)) was investigated. All exposures were conducted with carnauba wax aerosol present (‘unattached’ fraction < 1.5%). However, in Study 3, one group of animals was exposed without aerosol to give a high ‘unattached’ fraction (approximately 60%). Details of the study design are given in Table I.

Two control groups were used. Contemporary animals to each exposure group were taken as controls and lived as cage controls for the duration of the study (\(n = 217\)). Sham exposed animals (\(n = 268\)) consisted of three separate groups of contemporary animals who were exposed to carnauba wax only in the control exposure chamber for a period of 1080 h exposure conducted over 140 days to simulate the longest duration exposure of the radon/radon decay product exposed animals.

**Data analysis**

Statistical analysis of the tumour incidences was conducted using Peto (1974) and Peto et al. (1980) competitive risk methods. This included analysis of the incidence of all lung tumours (malignant and benign) and other non-lung pathology.

The analyses of the form of the dose rate and dose response relationships were based on proportional hazard excess relative risk models where relative risk (RR) is given by Equation 2.

\[
RR = 1 + f(\text{dose}), g(\text{dose rate})
\] (2)

The equation was fitted using the Peanuts program (part of the Epicure package). For the models that used the dose information, this was incorporated as either a time dependent covariate or a categorical variable. All animals were considered ‘at risk’ from the date of delivery. Animals that were removed from the study for other investigations were censored at the time of removal. In each analysis the quality of the fit of nested models was compared using a likelihood ratio test with the object of determining the best fitting, most parsimonious, model. In other words, the objective was to identify the model that best described the data using the least number of parameters.

The aims of the analyses were to reveal the shape of any dose response relationship and to investigate whether there was any dose rate effect. In each analysis the following models were compared: Null model (fits a single risk estimate to all data), a dose/dose rate factor model (fits separate risk estimates to each level of the factor – relative to a baseline), linear dose/dose rate response model, linear quadratic dose/dose rate response model, other models based on the combination of above.

All animals were kept in accordance with the Home Office Animals (Scientific Procedures) Act 1986 and the study followed the Guidelines for the Welfare of Animals in Experimental Neoplasia (UK
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- Mixed adenocarcinomas and squamous cell carcinoma.
- Exposed at high unattached fraction.
Results

Facility performance

The exposure facility proved to be very consistent in achieving the target cumulative doses and dose rates. Table I gives the actual cumulative exposures and dose rates achieved against the target exposures. For given target cumulative exposures, the mean cumulative exposure achieved was always within 10% of the target. For the dose rate this was always within 20% of the target.

Lung deposition

There was good correlation between exposure concentration and deposition of radon decay products ($^{218}$Po, $^{214}$Bi and $^{214}$Pb) in the rat lung. At low ‘unattached’ fractions (all exposures except Study 3 group 3) the absorbed dose to the rat lung from the deposited progeny was 1.5–1.9 mGy/WLM (this is assuming the energy is deposed to the whole of the lung mass). Lung deposition in the group exposed at high ‘unattached’ fraction (Study 3 group 3) was markedly higher (2–10 fold) than in the other groups. Measurements of deposition in the head and nose were also considerably (10 fold) higher at high ‘unattached’ fractions (Strong & Baker 1996, Baker et al. 1997). The results are in agreement with the predictions of the ICRP model of the respiratory tract (albeit for humans) in that ‘Unattached fraction’ (particles of around 1 nm) will deposit efficiently by diffusion and will therefore be largely removed in the nose and mouth (Bier VI 1999).

Early effects

The results of radon/radon decay product exposure on the lung epithelial cell proliferation and on the incidence of nuclear aberrations in alveolar macrophages have been published previously (Baker et al. 1997, Collier et al. 1996, 1997, Bisson et al. 1994). No further results on the incidence of nuclear aberrations are given in this paper.

There were no significant differences in proliferation rates in either bronchial or alveolar regions for the three control exposed groups of animals and for all further analyses these animals were treated as one group. In all animals, proliferation rates in bronchial epithelium were very low (0.07 ± 0.019% of cells labelled with BrdU, mean ± SE, $n = 103$) and were not significantly different between radon exposed animals and control animals (ANOVA). In addition there were no significant trends with either dose or dose rate for proliferation in this region.

Proliferation in alveolar epithelial cells was somewhat higher than in bronchial epithelium with the incidence of BrdU labelled cells in controls being 0.125 ± 0.022% ($n = 14$). In exposed animals proliferation was significantly elevated, with the incidence of BrdU labelled cells being 0.476 ± 0.047% ($n = 83$) (ANOVA $p < 0.005$). Figures 1 and 2 show alveolar

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Figure 1. Alveolar epithelial cell proliferation in rats as a function of cumulative exposure (WLM) exposed at a dose rate (exposure concentration) of 1000 WL. Proliferation (Labelling Index) was measured as the percentage of cells incorporating BrdU in vivo over 4 hrs. (data points are means $n = 3–14$ and error bars are Standard Error of Mean, $p$ level given indicates significance in ANOVA).
proliferation against cumulative exposure (WLM) and exposure concentration (WL).

Groups exposed at exposure concentrations of 1000 WL and at cumulative doses between 200 and 1600 WLM and groups exposed at exposure concentrations between 500 and 2000 WL and cumulative exposures of 1000 WLM all showed significantly elevated alveolar epithelial proliferation rates. There appeared to be an increase in labelling index with cumulative dose up to 1000 WLM in animals exposed to the same exposure concentration (1000 WL) (see Figure 1). This response decreased at higher cumulative doses such that in animals exposed at 3200 WLM at 1000 WL alveolar proliferation was not significantly elevated. Alveolar proliferation increased with exposure concentration (dose rate) for animals exposed at similar cumulative exposures (100 WLM and 1000 WLM) (see Figure 2). At cumulative exposures of 1000 WLM, proliferation was significantly elevated at exposure concentrations of 500 – 2000 WL, with a peak response at 1000 WL. At lower total cumulative exposure (100 WLM) elevated proliferation rates were only observed at an exposure concentration of 150 WL, with higher and lower exposure concentrations not showing significant elevation in proliferation rates. Hence it appears that alveolar proliferation increases with exposure concentration to a peak and then declines. This peak incidence increases with increasing exposure concentration, and the peak response position depends on total cumulative dose, occurring at a lower dose rate for lower cumulative doses.

**Histopathological findings**

The incidence of each lung tumour type (as number of animals bearing that tumour type) is given in Table I. The number of animals at risk, is fewer than the number of animals on study as a few animals from each group were taken for other research projects or were not available for full pathological examination.

**Pathological incidences – control groups**

There were no significant differences between either cage controls and sham exposed animals or between control animals from Study 1 or 3. As a result all control animal data was combined. The survival of all control animals (n = 496) was included up to their removal from the study for any reason and tumour/ non tumour incidences were available for 479 animals. The incidence of fibrosis in the control animals was <1%.

**Pathological incidences – dose response at 1000 WL (Study 1)**

Significantly elevated incidences of bronchoalveolar adenocarcinomas and bronchial adenocarcinoma were found in Study 1 at cumulative exposures of 200, 1600 and 3200 WLM (see Figure 3, levels of significance given in the figure). In addition a significantly elevated incidence of squamous cell carcinoma was observed at 1600 WLM in this study.
When the incidence of all primary lung malignancies was considered, significantly elevated incidences were observed at 200, 1600 and 3200 WLM ($p < 0.005$).

The incidence of benign adenomas was significantly elevated in all exposure levels in Study 1 (see Figure 4, $p < 0.005$). Cumulative exposure level had no significant effect on the incidence of benign adenomas.
papillomas. Overall, the incidence of all benign tumours was elevated at all exposure levels, due to the significant effect on the adenoma incidence ($p < 0.005$).

The most frequently occurring non-lung tumours in these exposure groups were fibrosarcomas (35 found) and leukaemias (30 found), however neither finding showed any relationship with radon/radon decay product exposure.

Fibrosis incidences in all groups were lower than in the control group and showed an average incidence of 0.2%.

Pathological incidences – effect of dose rate at 1000 WLM (Study 2)

At relatively high doses (1000 WLM), significantly elevated incidences of bronchoalveolar adenocarcinoma were observed at exposure concentrations of 250, 1000 and 2000 WL. For bronchial adenocarcinoma, incidences were significantly elevated over controls at all exposure concentrations and significantly elevated squamous cell carcinomas incidences were observed at 1000 and 2000 WL. Overall the incidence of primary lung malignancies was significantly elevated at all exposure concentrations (see Figure 5, $p < 0.005$).

For benign tumours, papilloma incidences were significantly elevated above control levels at 250, 1000 and 2000 WL, adenoma incidences were significantly elevated at exposure concentrations of 250, 500 and 2000 WL and the combined effect was that the incidence of all benign lung tumours was significantly elevated above control levels at all exposure concentrations (see Figure 6, levels of significance given in Figure).

When considering the findings outside the lung, the incidence of fibroma was significantly elevated ($p < 0.05$) by four-fold in the animals exposed at 1000 WL, with four cases occurring rather than the one expected from control incidences. The incidence of renal adenocarcinoma was significantly higher than controls for animals exposed at 500 WL ($p < 0.05$) with 3 cases occurring where fewer than 1 would have been expected from control incidences. In addition, the animals exposed at 500 WL also showed a significant incidence of hyperkeratosis ($p < 0.05$), with two cases occurring when less than one would have been expected from control incidences.

Pathological incidences – effect of dose rate at 100 WLM and unattached fraction (Study 3)

At lower cumulative doses (100 WLM), the incidence of squamous cell carcinomas was elevated at 150 WL ($p < 0.05$) and the incidence of bronchoalveolar adenocarcinomas was elevated at 1000 WL.

![Figure 5. Primary malignant lung tumour incidence in rats following exposure to radon/radon progeny at a cumulative dose of 1000 WLM and exposure concentrations of 250–2000 WL (Study 2). Significant differences in incidence from controls (see text for methods) are indicated according to the key. ### Total tumour incidence (all benign or all malignant) significantly different from controls ($p < 0.001$); ## Total tumour incidence (all benign or all malignant) significantly different from controls ($p < 0.01$); *** Individual tumour type incidence significantly different from controls ($p < 0.001$); ** Individual tumour type incidence significantly different from controls ($p < 0.01$); * Individual tumour type incidence significantly different from controls ($p < 0.05$).]
Overall, the incidence of primary lung malignancies was significantly elevated above control levels at all dose rates, including the exposure at high ‘unattached’ fraction (see Figure 7, levels of significance given in the Figure).

Overall, incidences were markedly lower than at higher cumulative exposures (1.5–3.0% compared with 5–20% at 1000 WLM). The incidence of adenomas, and as a consequence all benign tumours, was significantly elevated above control levels in all exposure groups (see Figure 8, levels of significance given in the figure).

For all lung tumour types (malignant and benign) and for non-lung histopathology, the incidence of findings was compared for the two groups of animals exposed at 150 WL dose rates (high and low unattached fractions). For all tumour types except leukaemia there was no significant difference between the two groups. For leukaemia there was a significantly lower ($p < 0.05$) incidence in the high ‘unattached’ group, compared with the low ‘unattached’ group. However the low ‘unattached’ group leukaemia incidence was not significantly different from that of controls. The incidence in the high ‘unattached’ group was lower than that in the controls, although the difference was not significant.

The incidences of mammary fibroadenomas and malignant trichoepithelioma were significantly elevated above control levels in the group exposed at the high ‘unattached’ fraction (150 WL) ($p < 0.00895$ and $0.037$ respectively). For mammary fibroadenomas in this group, incidences were nearly four-fold higher than expected from control incidences with 5 cases occurring in the exposure group of 184 animals. For trichoepithelioma incidences were elevated approximately 6 times over that found in controls, with 2 cases being found in the group.

**Dose response and dose rate relationships**

An initial analysis demonstrated that tumour subtype based analysis was not practical due to the paucity of tumours. So the analysis was conducted on all primary malignant lung tumours and on all primary lung cancers (all primary malignant tumours plus all benign tumours). The control data was analysed as before for differences between exposure group (those exposed as a part of Study 1 and Study 3) and whether animals were sham exposed or cage controls. No differences were found between the controls from any of these sub-groups and so all further analysis regarded the combined data from the controls. It should be noted that the tumour incidences in the control animals were extremely low and so it was probably beyond the power of this study to detect all but the most pronounced of effects between the different control groups.

**Shape of the dose response curve (Study 1)**

For both responses (all malignant lung tumours and all primary lung tumours) the relative quality of fit of
a range of models, including linear, linear quadratic and categorical was assessed. The dose response was best fitted using a dose category model. That is a model in which individual constant relative risk values are derived for all animals in each of 6 exposure categories (0, <200, <400, <800, <1600 and <3200 WLM). A linear dose response model was found to fit better than a linear quadratic model.
for both analyses (malignant lung and primary lung tumours), but was not as good as the categorical model. The parameters of the best fitting model for all primary lung tumours are given in Table II. The dose category model provides the best fit because of the shape of the dose response relationship with the incidence of tumours in the 200 WLM group being higher than that for 400 and 800 WLM and then increasing again at doses of 1600 WLM and higher. It is not possible to speculate as to whether the curve is in reality a smooth response with dose and in this study we have seen a lower than expected incidence in the 400 and 800 WLM groups/a higher than expected incidence in the 200 WLM exposed groups or whether the shape of the response observed is the true response.

**Shape of the dose rate response curve at high doses (Study 2)**

For all malignant lung cancers the best model contained only a single factor to denote different risks for the exposed animals, as a single group from the control animals. The relative risk for the exposed compared with the controls was 35.31 with a lower 95% confidence interval (CI) value of 6.64 (the upper bound value could not be derived). For all lung cancers the best model was a dose rate category factor (0, 250, 500, 1000, 2000 WL). The parameters of the best fitting model for all primary lung tumours are given in Table III.

**Shape of the dose rate response curve at low doses (Study 3)**

Both the analysis of all malignant primary and all primary tumours revealed that a statistically significant difference could only be detected in the risk between the control and exposed animals. No difference in risk was identified between the groups exposed at different rates. For the analysis of all malignant primary lung tumours the risk of the exposed animals relative to the controls was 12.61 (95% CI 1.85 – 25.36) while the risk for all primary lung tumours was 12.68 (95% CI 1.94 – 25.86).

Table II. Parameter summary for best fitting model for Study 1, dose response (all primary lung tumours).

<table>
<thead>
<tr>
<th>Dose category</th>
<th>Estimate of relative risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200 WLM</td>
<td>8.27</td>
<td>1.55 – 58.35</td>
</tr>
<tr>
<td>≤ 400 WLM</td>
<td>3.37</td>
<td>-0.058 – 29.52</td>
</tr>
<tr>
<td>≤ 800 WLM</td>
<td>10.18</td>
<td>1.93 – 71.87</td>
</tr>
<tr>
<td>≤ 1600 WLM</td>
<td>11.44</td>
<td>2.32 – 79.49</td>
</tr>
<tr>
<td>≤ 3200 WLM</td>
<td>35.38</td>
<td>8.71 – 234.8</td>
</tr>
</tbody>
</table>

Table III. Parameter summary for the best fitting model for Study 2, dose rate response (all primary lung tumours).

<table>
<thead>
<tr>
<th>Dose rate category</th>
<th>Estimate of relative risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 WL</td>
<td>60.98</td>
<td>15.02 – 412.9</td>
</tr>
<tr>
<td>500 WL</td>
<td>13.42</td>
<td>2.39 – 97.58</td>
</tr>
<tr>
<td>1000 WL</td>
<td>30.63</td>
<td>6.72 – 213.98</td>
</tr>
<tr>
<td>2000 WL</td>
<td>22.94</td>
<td>5.67 – na</td>
</tr>
</tbody>
</table>

No statistically significant difference was found in either tumour category between the animals exposed at high or low ‘unattached’ fractions.

**Shape of the dose/dose rate response curve from all data**

For the analysis of all the data together a six-level dose rate factor with categories 0, <16, <258, <730, <1360 and <1880 WL was used and also a six-level dose factor with categories 0, <200, <400, <800, <1600 and <3200 WLM. The dose category factor model provided the best fit for both the malignant primary lung cancers and all primary lung cancer incidences. Table IV gives the parameter summary for the best fitting model based on all data (primary lung cancers).

Further investigation revealed that among the models that attempted to fit some sort of dose response relationship, the one that provided the best fit for both analyses (malignant lung tumours and all primary lung tumours) had a separate linear dose response function for each dose rate group. The parameters for this analysis are summarized in Table V.

**Discussion**

Three research groups have contributed to the majority of the knowledge of the effects of radon/radon decay product exposure on animals: CEA, PNNL, and these current studies at Harwell. The CEA and Harwell studies used Sprague Dawley rats (CEA \( n = 13000 \) and Harwell \( n = 2000 \)), whereas those at PNNL used mice, hamsters, Wistar rats and dogs. Differences in the sensitivity of different strains/species to lung tumour induction have been observed. For example, Syrian hamsters were very resistant to lung tumour induction by radon/radon decay products when compared with Wistar rats (Khan et al. 1995) and Groch et al. (1997) reported differences in susceptibility between two strains of mice. The majority of the studies have been conducted in rats. The very low control incidence of malignant lung tumours in rats (CEA 0.6% males, 0% females; Harwell 0.4% in males) and the
The current studies show a similar dose response relationship for the Harwell male rats with the peak incidence for all primary lung tumours occurring at a similar cumulative exposure but being somewhat lower in magnitude (25%). In CEA’s studies, exposures as low as 25 WLM resulted in significant excess lung tumours (Monchaux & Morlier 2000). In the current studies the lowest cumulative exposure was 100 WLM. At this level, whilst overall tumour incidences were lower than at higher cumulative exposures, they remained significantly elevated over control incidences. In all three Harwell exposure groups, the major effects were on benign bronchial adenoma and malignant bronchial and bronchoalveolar adenocarcinomas. Significant elevations of these tumour types were seen at doses as low as 100 WLM. Responses for other tumour types in the lung were not as sensitive and only became significant at higher doses, such that for exposures at 1000 WLM all benign and malignant lung tumour incidences were significantly elevated.

At very high exposure levels (>1000 WLM), which do not mimic human domestic exposure, excesses in non-malignant lung diseases (lung fibrosis and emphysema) were observed in studies at CEA and PNNL. These resulted in significant life shortening and as lung tumours occur relatively late in the life of the rat, excesses in lung malignancies declined at high exposure levels. PNNL observed no apparent threshold for lung cancer induction, but CEA’s studies at low cumulative exposures and exposure rates showed no evidence of lung tumour induction. For example, rats exposed at 25 WLM over 18 months showed no excess of lung tumours (incidence 0.6%), but those exposed to the same cumulative exposure using a higher concentration showed no evidence of lung tumour induction. For example, rats exposed at 25 WLM over 18 months showed no excess of lung tumours (incidence 0.6%), but those exposed to the same cumulative exposure using a higher concentration over a shorter period (4–6 months) showed a significantly elevated tumour incidence. Animals exposed to radon/radon decay products in this study showed no elevation in fibrosis incidence over control animals (even in the groups exposed at 1600 and 3200 WLM).

The analyses of the dose response data generated in Study 1 for both malignant lung cancers and all primary lung cancers showed a model in which separate risk coefficients were derived for each level of categorical dose provided the best fit. The relative risk coefficients of the model indicated a general upward trend in the risk with increasing dose in all but one of the dose categories, however this trend was not sufficiently strong for either a linear or a quadratic dose response model to provide a better fit than the categorical model. A reanalysis including additional data for animals exposed at 1000 WLM from Studies 2 and 3 gave very similar results. The analyses of the primary malignant tumours for the high dose rate study (Study 2) could only detect a
difference in the incidence of lung cancers between all the exposed (as a single group) and all the control animals. No statistically significant differences could be detected between the various exposure rate groups. The analysis of all primary lung tumours did however, find a difference between the exposure rate groups. There is an indication from the parameter estimates that at a given dose of 1000 WLM, the risk decreases with increasing exposure rate. For the low dose rate study (Study 3), the separate analyses of both the primary malignant tumours and all primary tumours could only detect a difference in the incidence of lung cancers between exposed and control animals. No statistically significant difference could be detected between the various exposure dose rate groups.

In a recent series of experiments at CEA using 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 decreased with decreasing exposure concentration (Monchaux & Morlier 2002), confirming the results obtained by CEA at lower exposures. Recently the CEA, Harwell and PNNL data has been combined and analysed by staff at Forschungszentrum für Umwelt und Gesundheit (GSF) Neuherberg. This combination into larger data sets increases the statistical power of the analysis. Their analysis confirms that for high cumulative exposures, the lifetime excess absolute risk (LEAR) increases with increasing exposure durations and for low cumulative exposures the opposite trend occurs (Kaiser et al. 2004). All these data suggest that the induction of lung cancer results from a complex interplay between cumulative dose and dose-rate, with an optimal combination of these two parameters, i.e., a combination of cumulative dose and exposure concentration that results in a maximum risk of lung tumour 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 suggest that there is a watershed at cumulative exposures of about 50 WLM. Below this exposure, decreasing the exposure concentration or protracting the time over which the dose is delivered, results in a reduction in the lung tumour risk. Above this level the converse is true with decreasing exposure concentrations or protracting the exposure time resulting in an increasing lung cancer risk (Monchaux 2002).

These data are consistent with that of underground 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 et al. 1995). The data from Harwell and PNNL confirm the CEA results for exposures at levels well above 50 WLM, but only CEA data is available for exposures below this level. Harwell studies at 100 WLM cumulative exposure have demonstrated positive dose rate effects for broncho-alveolar adenocarcinomas indicating that the ‘watershed’ may be slightly higher for this one tumour type. In the Harwell studies all other tumour types showed no effect of dose rate, although the exposure did result in elevated incidences of benign adenoma. It has been postulated that the reasons for the existence of an apparent watershed can be related to the hits per cell. When cumulative exposures are sufficiently low, and concentrations low or protraction high, there is an extremely low probability that any cell would be traversed by more than one alpha particle (Bier VI 1999). At these levels the extent of the damage to individual cells is not related to the total dose/dose rate, hence the probability of detrimental effects occurring shows a linear relationship with total dose. At higher doses, multiple cell traversals occur with significant probabilities. These multiple hits to individual cells can result in additional damage to the cells that can result in decrease efficiency of repair, increased cell killing and possibly diffusible clastogenic factors which can affect other untraversed cells. All of these effects modify the shape of the dose-rate response curve so that at higher doses inverse dose responses are observed that are diminished or do not occur at lower doses (Monchaux & Morlier 2000, Morlier et al. 1992).

Both PNNL and CEA have observed that, latency periods are decreased for older rats, or, in the rat, lung tumours generally occur between 800 and 900 days of age regardless of age at exposure. Co-analysis of the CEA, Harwell and PNNL data have shown that animals exposed later in life have substantially lower LEAR than animals exposed in early life (<150 days) (Heidenreich et al. 2004). In considering the relationship between dose rate and exposure it is important to include a consideration of the age of the animals at exposure. When comparing equivalent doses at high and low dose rates there is an implication that the animals receiving the lower dose rate will have received some of their dose a considerably higher ages than those at the higher dose rate. In this series of studies, the two experiments on dose rate effects were conducted on animals of similar ages. For the dose rate at higher doses study (study 2) the doses were accumulated over periods of between 4 and 40 days. The median survival of exposed animals in this study was 778 days hence the 36 days maximum difference in exposure durations represents a very small fraction (<5%) of the total period ‘at risk’ and the differences in age at exposure are unlikely to be significant for the different exposure groups. The same situation is
WLM resulted in a doubling of benign mammary tumours with the Wistar rat at PNNL, exposures at 640 WLM compared with 30% observed normally in controls. In the 3 laboratories. Increases in leukaemia incidences following exposure to radon/radon decay product exposure have been reported in some studies conducted in all three laboratories including the current Harwell studies. Renal tumours have also shown increases in incidence, significantly so for some studies from 2 of the 3 laboratories. Increases in leukaemia incidences following exposure to radon/radon decay product exposure have not been observed in experimental animals by any of the laboratories. Various other tumours have been observed at slightly elevated levels, but not consistently across the three laboratories. Co-analysis of CEA, Harwell and PNNL data has indicated that radon/radon decay product exposure results in additional lethal effects over lung tumours (Kaiser et al. 2004).

The principal finding of all the animal studies has been that of lung tumour induction. At high exposure levels non-malignant lung damage reduced lifespan at both CEA and PNNL. In most animal studies all tumours, whether occurring in the lung or not, are investigated and reported. The control incidences of non-lung tumours in experimental animals are generally considerably higher than those of lung tumours and this reduces the power of the studies making significant excesses induced by radon/radon decay products almost impossible to detect. In spite of these difficulties, significant increases in mammary tumour incidence following radon/radon decay product exposure have been reported in some studies conducted in all three laboratories including the current Harwell studies. Renal tumours have also shown increased incidences, significantly so for some studies from 2 of the 3 laboratories. Increases in leukaemia incidences following exposure to radon/radon decay product exposure have not been observed in experimental animals by any of the laboratories. Various other tumours have been observed at slightly elevated levels, but not consistently across the three laboratories. Co-analysis of CEA, Harwell and PNNL data has indicated that radon/radon decay product exposure results in additional lethal effects over lung tumours (Kaiser et al. 2004).

In the CEA studies in Sprague Dawley female rats, an excess of mammary tumours was observed over controls at 1600 WLM with incidences of 78% compared with 30% observed normally in controls. With the Wistar rat at PNNL, exposures at 640 WLM resulted in a doubling of benign mammary tumour incidence. The current studies at Harwell used male rats with a much lower control incidence of mammary tumours (1%) than female animals. In all groups, mammary tumour incidences were not significantly different from controls, with the exception of animals exposed at 100 WLM, with high ‘unattached’ fractions where a four-fold increase in mammary tumour incidence over control levels was observed.

PNNL studies showed slight but significant increases in kidney carcinomas, but their carrier aerosol was uranium ore dust that may account for this finding. A slight, but not significant excess of kidney tumours was reported by CEA in animals exposed up to 1000 WLM, (Monchaux personal communication). In one of the three studies conducted at Harwell a significantly elevated incidence of renal adenocarcinomas was observed in animals exposed at 500 WL and 1000 WLM (3 cases observed out of 50 animals where 1 was expected). Co-exposure to uranium ore dust did not occur at CEA or Harwell, so there is an indication of a slight increase in kidney tumours associated with radon/radon decay product exposure from all three groups.

In the Harwell studies, significant excesses in fibroma, hyperkeratosis and malignant trichoeplithelioma were observed in single groups of animals exposed in Study 2 at 1000 WLM, 500 WL and in Study 3 in the high ‘unattached’ fraction group respectively. Neither of the other two laboratories has reported excesses of these lesions following exposure to radon/radon decay products. In studies at CEA, the only other findings were slight and non-significant excesses in osteosarcoma and liver tumours.

At high ‘unattached’ fractions, the current studies showed a markedly higher deposition of radon decay products in the nasal passages. This is possibly the cause of the lesions found in the noses of animals exposed at high ‘unattached’ fractions (PNNL studies). The higher deposition may also account for the increased skin (trichoeplithelioma) incidences observed in this group.

Conclusions
A facility was constructed for the continuous exposure of rats to radon/radon decay products in a recirculating environment. The facility showed excellent stability and reproducibility. Over the course of 4 years 1850 male Sprague Dawley rats were exposed to control aerosol or a mixture of radon/radon decay products attached to carrier aerosol. Deposition of radon decay products in the lung was directly proportional to the exposure concentrations. Early effects on cell proliferation and nuclear aberrations were found to be related to time since exposure, animal age and exposure concentrations.
Incidentes of primary malignant lung tumours were significantly elevated above control groups in 11 out of the 13 groups exposed to radon/radon decay products. For benign tumours, incidences were significantly elevated above control levels in all 13 groups exposed to radon/radon decay products. The most frequent lung tumour in radon/radon decay product exposed animals was benign adenoma (incidence 4.68% overall for all exposed animals, 0.2% in controls). Malignant tumours of the bronchoalveolar adenocarcinoma and bronchoadenocarcinoma types occurred at overall incidences of 1.9% and 1.7% in radon/radon decay product exposed animals, whereas control incidences were 0.2% and 0%. Malignant squamous cell carcinomas and benign papillomas were less frequent with incidences of 1.1 and 0.84% in radon/radon decay product exposed animals compared with incidences of 0% for both tumour types in control animals.

Analysis of the dose and dose response curves indicated that there was an increasing risk with increasing cumulative exposures, but the power of the study was insufficient to detect whether this was a linear or a linear quadratic effect. In the high dose rate study (Study 2) analysis indicated that the dose rate was having an effect on the response, but not in a consistent way.

Combination of the results of this study with those of animals exposed at CEA and PNNL by other authors have added considerably to the power of the analysis and have demonstrated that for high cumulative exposures, the lifetime excess absolute risk (LEAR) increases with increasing exposure durations and for low cumulative exposures the opposite trend occurs (Kaiser et al. 2004). The results 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 combined data suggest that there is a watershed at cumulative exposures of about 50 WLM. Below this exposure, decreasing the exposure concentration or protracting the time over which the dose is delivered, reduces the lung tumour risk. Above this level the converse is true with decreasing exposure concentrations or protracting the exposure time resulting in an increasing lung cancer risk (Monchaux 2002).

Significantly elevated incidences of fibroma, renal adenocarcinoma, hyperkeratosis, mammary fibroadenomas, malignant trichoblastoma occurred in single groups of radon/radon decay product exposed animals, but the power of the study was insufficient to detect dose or dose response relationships. Analysis of the combined data from all animal studies by Kaiser et al. (2004) has indicated that radon/radon decay product exposure results in additional lethal effects over lung tumours (Kaiser et al. 2004).

Acknowledgements

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