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RISKS FROM RADON PROGENY EXPOSURE: What We Know, and What We Need to Know*

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INTRODUCTION

Scientific interest in radon spans 90 years since it was first discovered by Dorn (1) in 1900 and detected in air by Elster & Geitel (2) in 1901. It is an inert radioactive gas that occurs naturally in the environment. Although there are 25 known isotopes of radon, only three occur naturally in the environment. These isotopes, ^{219}Rn, ^{220}Rn and ^{222}Rn, arise as a result of radioactive decay series beginning with either uranium or thorium isotopes. From dosimetry and risk perspectives, ^{219}Rn is unimportant because of its very low concentrations in air, due mainly to the scarcity of its parent radionuclide, ^{235}U, and its very short half-life (3.9 seconds). Radon-220 (thoron) is a radioactive progeny (or daughter) of naturally occurring ^{232}Th, as is ^{222}Rn, a progeny of ^{238}U. Radon-220 and ^{222}Rn are produced in similar quantities worldwide because of the similarities in the crustal abundances of uranium and thorium (about 25 Bq/kg earth) (3). However, differences in half-lives and aerosol properties between the two isotopes produce about a fivefold

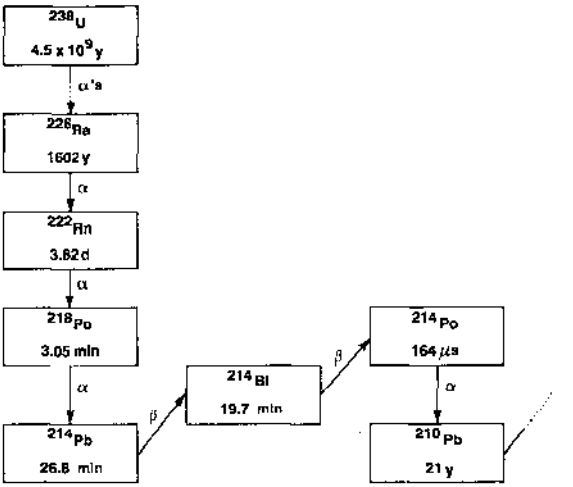


Figure 1 Stylized decay scheme containing ^{222}Rn and its short-lived progeny. Several radioactive species within the complete decay chain, which begins with ^{238}U and ends with ^{206}Pb, were omitted, as were several minor branches of decay.

greater concentration of ^{222}Rn in indoor air compared to ^{220}Rn (4). Additionally, the alpha radiation dose to lung airways from ^{220}Rn progeny is less than for equivalent amounts of ^{222}Rn progeny so that under ordinary circumstances, exposure of the respiratory tract to ^{220}Rn and progeny is less than 20% of that from ^{222}Rn progeny (3). This review therefore focuses on the risks from exposure to ^{222}Rn and its progeny.

A simplified decay scheme for ^{238}U through the short-lived biologically significant Rn progeny is shown in Figure 1. The presence of ^{222}Rn is controlled by the concentration of the parent ^{226}Ra in soil, rock, or water. Radon itself is the heaviest of the noble gases, and is odorless, colorless, and almost chemically inert. As a noble gas, Rn is relatively free to move within the original matrix in which it was formed, and subsequently can reach air and water to which people can be exposed. Decay of Rn produces progeny that are chemically active nongaseous species, with relatively short half-lives. An important early finding linked the health risk associated with exposure to Rn and Rn progeny to the radiation doses from the Rn progeny radionuclides, particularly the α-emitters ^{218}Po and ^{214}Po, and not to direct exposure to the Rn gas. W. F. Bale called this to the attention of the scientific community in his famous 1951 memo to the file during his term of service to the US Atomic Energy Commission (5). Confirmation that more than 95% of the α-radiation dose is indeed due to the Rn progeny has been subsequently made by numerous theoretical dosimetry models. Rn-222, an inert gas with a 3.8 day

half-life, does not deposit or decay within the respiratory tract to any significant extent. The progeny on the other hand, being particulates themselves or being attached to other aerosol particles, deposit on the surfaces of the respiratory tract. For simplicity, all future reference will be to Rn progeny and will mean dose, effects, and risks associated with exposure to the Rn-progeny-containing aerosols.

Recognition of the biological importance of the Rn progeny mandated measurements of the short-lived Rn progeny in the atmosphere. Thus, field methods were developed in the mid-1950s to measure the quantities of the individual progeny radionuclides in mine atmospheres (6, 7). These methods represented an important advance over earlier measurements of Rn gas alone. Radon data rarely are valid for predicting the concentrations of Rn progeny in any atmosphere because the short half-lives of the progeny, together with physical processes that remove Rn-progeny-containing aerosols from the atmosphere, tend to result in variable amounts of the progeny in the air at any given time, i.e. quantities less than the equilibrium concentration. To relate atmospheric concentrations of the Rn progeny to the dose delivered to the human lung, a special quantity was developed, potential alpha energy concentration (PAEC). Potential alpha energy is the total alpha energy emitted by an atom as it decays through its radioactive series through ^{210}Po (only the alpha energy was considered to be of radiobiological importance). The most commonly used unit of PAEC is the Working Level (WL), which is defined as any combination of short-lived Rn decay products that will result in the emission of 1.3×10^5 MeV of α energy per liter of air. One WL corresponds approximately to the PAEC of short-lived Rn progeny that are in radioactive equilibrium with a concentration of 3700 Bq/m^3 of air. A Working Level is approximately the amount of α energy emitted by the progeny in equilibrium concentration with 100 pCi/L of the parent ^{222}Rn. The SI unit for PAEC is J/m^3. Cumulative exposure is expressed in the unit, Working Level Month (WLM), which is equal to exposure at 1 WL for a period of 170 hours, a typical "work month". For exposure to varying concentrations of Rn progeny, the cumulative exposure, in WLM, is the sum of the products of PAEC $\times$ time of exposure. For nonoccupational exposures, a month is equivalent to 720 hours, and therefore, an environmental exposure to 1 WL for 720 hours is equivalent to 4.235 WLM. A summary of quantities and units pertinent to Rn and progeny is given in Table 1.

The quantity of a radionuclide is conventionally specified by its radioactivity, defined as the number of nuclear transformations that occur per unit of time. The SI unit for activity is the becquerel (Bq) and is equal to one nuclear transformation (or disintegration) per second. The traditional unit of activity, the curie (Ci) is equal to 3.7×10^{10} disintegration per second. Environmental levels of radon are generally described in terms of picocuries (pCi), where 1

Table 1 Physical quantities and units relevant to Rn and Rn progeny

Quantity	SI Unit	Traditional unit	Conversion factor
Activity	becquerel (Bq)	curie (Ci)	1 Ci = 3.7×10^{10} Bq
Concentration	Bq/m^3	pCi/L	1 pCi/L = 37 Bq/m^3
PAEC	J/m^3	Working level (WL)	1 WL = 2.08×10^{-5} J/m^3
Exposure	$J\text{-}s/m^3$	WLM	1 WLM = 12.97 $J\text{-}s/m^3$
Exposure Rate	J/m^3	WLM/y	1 WLM/y = 4.11×10^{-7} J/m^3

pCi = 10^{-12} Ci. Concentrations of radon in air are given in SI units of Bq/m^3, and in pCi/L for the traditional units.

As early as the sixteenth century (8) a high incidence of lung disease was recognized among certain underground miners in eastern Europe. This disease was later diagnosed as lung cancer in the mining populations in Schneeberg and in the Erz mountains (9–11). The causative relationship between high radon concentrations in mine air and excess incidence of lung cancer in miners was not determined through epidemiological research until fairly recently (12, 13). Even more recently, many underground miner populations have been studied with respect to exposure to Rn progeny and the observed incidence of lung cancer. These populations have included both uranium miners (14–18) and other hard rock miners (19–27). As a result, it is now generally accepted that inhalation of Rn progeny has led to increased incidences of lung cancer in underground miner populations, and that the magnitude of the increased cancer incidence is related to the cumulative exposure, and therefore the cumulative radiation dose, to the miner.

Although the uranium miner experience is an unfortunate and tragic lesson in alpha-emitter radiobiology by itself, the present level of scientific and public concern regarding the risks from inhalation exposure to Rn progeny has been exacerbated by the discovery of high levels of Rn within the indoor environments of domestic dwellings (28, 29). Within a fairly brief period of time, the potential health implications of inhaling Rn progeny within home environments have become more widely recognized, prompting regulatory authorities from different countries to set standards for exposure levels within domestic environments (30). Recent consensus scientific committees have concluded that from 50% to 70% of the radiation dose received by individuals from the natural radiation environment is due to alpha irradiation of the bronchial epithelium of the lung by radon and radon progeny (31–34).

Despite the awareness among most radiation protection professionals of the contribution of Rn progeny to our radiation dose commitment, scientific and political debate continues as to the risks associated with Rn exposure in the home. The controversy persists primarily because the risk analyses for inhaled Rn progeny have all been derived from epidemiological studies of miner

Table 2 Differences between exposure in Rn in mines and homes

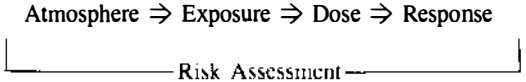
Variable	Mines	Homes
Subjects	Adult males (20–50 yr)	Males and females, all ages
Exposure period	Work week (8 h/d, 5d/wk)	Lifetime
Rn exposure levels	High	Variable down to background
Atmosphere	Ore and rock dust, diesel exhaust	Relatively clean, potentially with cigarette smoke, cooking fumes
Prevalence of smoking	Higher than average	Average

populations. Exposures to Rn and Rn progeny occurring in mine environments and in homes differ significantly, and these differences can potentially affect the associated risks. Several of these differences are summarized in Table 2.

This review aims to present the state of our knowledge regarding exposure to Rn progeny aerosols, the attendant radiation doses, and the risks associated with such doses. We focus on exposure of the general population within domestic environments; however, because the estimates of risk arise from the data on miner populations, the important uncertainties that must be considered in extrapolating from miners to the general population (e.g. Table 2) are featured, along with the current knowledge base and the needs for further data and understanding.

WHAT IS REQUIRED FOR RISK ASSESSMENT OF INHALED RADON?

Risk assessment is the process of characterizing and quantifying potential adverse health effects that may result from exposures to harmful physical or chemical agents in the environment, in this case Rn progeny. The process requires knowledge of each of the component parts that contribute to risk. For inhaled toxicants such as Rn progeny, the components are illustrated thus:



As mentioned previously, the primary scientific issue relating to inhaled Rn progeny is how risk factors based on epidemiological studies of exposed miner populations can be applied to the general population. To do this, one

needs to define the physical, chemical, and biological factors that differ either qualitatively or quantitatively between the two exposure modalities, and evaluate the effects of these differences on either the expected exposure-dose or the dose-response relationships. Because of the lack of convincing data to date for human effects from Rn progeny exposures in the general population, these relationships (and their associated uncertainties) are generally evaluated through the use of theoretical models. Most of this paper is organized according to the four components of the Rn risk assessment—atmosphere, exposure, dose, and biological response—to facilitate presentation of the many differences between the miner and home exposure scenarios, and to discuss the implications of these differences. Recent monographs provide the interested reader with more detailed and broader discussions (4, 31, 35–40).

RADON AND RADON PROGENY IN THE ATMOSPHERE

Environmental Levels of Rn and Progeny

The source of Rn and Rn progeny in the atmosphere is radium present in soil, rock, water, or building materials. Radium-226 concentrations within soils vary over several orders of magnitude but are generally between 10 and 50 Bq/kg, with an estimated average concentration of 25 Bq/kg (3). Radium levels in sea water are four to five orders of magnitude lower than in most soils, and thus do not contribute significantly to environmental levels of Rn (41). Radon formed in rocks and soils is released only partially to air and water by mechanisms of diffusion, convection, and the general flow of air and water. Ordinarily, about 90% or more of the Rn formed in solids does not escape into air or water (3). Soil porosity and moisture content affect Rn transport rates significantly (42). The 3.8 day half-life for radiological decay of ^{222} Rn also limits its diffusion distance. It has been estimated that 90% of Rn decays by the time it has migrated 5 m in air, 5 cm in water, and 2 m in soil (3).

Although measurement of Rn concentrations in homes dates back to the 1950s (43), most studies were done after 1970 (3, 31, 44). The results of 40 studies that included over 96,000 homes and apartments from 20 countries are summarized in UNSCEAR 1988 (31). From these studies came the following conclusions:

1. Rn and Rn progeny concentrations could be described by log-normal distributions, with geometric standard deviations ranging from 1.6 to 5.2.
2. The medians of the Rn concentrations ranged from 4 Bq/m^3 in Poland (45) to about 30 Bq/m^3
3. The source of Rn in many of the houses with the highest Rn concentrations was the high Rn entry rate from the soil, and was not due to the high Rn

exhalation rates from building materials or high Rn concentrations in drinking water.

4. Because of the influence of Rn entry into dwellings via soil, Rn concentrations in houses were generally higher than those measured in multistory apartments above the ground floor.
5. The population-weighted mean of the indoor Rn concentrations was 51 Bq/m^3.

To put the levels of Rn and Rn progeny measured in domestic environments in perspective requires comparison with those present in mine atmospheres. Unfortunately, such a comparison is not simple because major changes in Rn/Rn-progeny concentrations have occurred over the past 40 years, mainly due to the implementation of increasingly effective ventilation systems in the mines. Estimates of the Rn exposure levels in the ancient mines of Schneeberg and Joachimsthal indicate that the levels were within the range of 100,000–3,000,000 Bq/m^3, four orders of magnitude higher that those typically found in homes (48–50). Holaday estimated that the Rn progeny concentrations ranged from 10 to 180 WL (51). Between 1870 to 1940 over 50% of miners died of lung cancer. By 1940, ventilation had been employed in the eastern European mines and the Rn concentrations were much lower (51). High Rn levels were also found in unventilated mines in Utah and Colorado in the early 1950s, with median concentrations being about 100,000 to 200,000 Bq/m^3, respectively (51). Rn progeny concentrations were probably within the range measured in the European mines, 2–200 WL.

In his paper on the history of exposure of miners to Rn, Holaday states:

> A most significant step in controlling exposure to radon daughters was taken at the Seven States Uranium Mining Conference held in Salt Lake City, 22–23 February 1955. This meeting recommended that all states adopt a tentative working level of 10^{-10} Ci/l of radon at equilibrium with its daughters. . . . for practical purposes the recommended standard was equivalent to one Working Level.

Improvements in both mechanical and natural ventilation continued during the 1950s such that only 29% of the uranium mines surveyed in 1961 had levels greater than 10 WL; this decreased to 1% by 1965 (51). Current limits on exposure to Rn progeny in mines, as enforced by the US Mine Safety and Health Administration, are a maximum annual exposure limit of 4 WLM, and a maximum concentration level of 1 WL. Annual average Rn progeny concentrations therefore must be kept below 0.3 WL. In more recent data on uranium miner exposures, the average annual cumulative exposure from 1980–85 was between 0.83 and 0.97 WLM, with over 60% of the miners accumulating less than 1 WLM/year (52). Records of lifetime exposures since

1967 (when mine operators began keeping records of individual employee exposures) showed that the vast majority of the miners had accumulated ≤ 5 WLM, with very few > 30 WLM, and none above 100 WLM (52). Thus, with the reduction in Rn progeny levels in mines, and the discovery of relatively high levels in homes, Rn progeny levels within these two environments now overlap.

Aerosol Properties of Rn Progeny

Early studies established two different types of aerosols of radon progeny—attached and unattached. Aerosol behavior of most of the progeny is similar to that of ordinary ambient aerosol particles in the atmosphere. Therefore, because radon progeny atoms are created one at a time from the parent Rn gas, scientists have assumed that these radon progeny atoms are attached to the already present atmospheric aerosol particles. This assumption is supported by measurements of the particle-size distributions of Rn progeny, as summarized by Hopke (53).

The second, more highly diffusive species, the unattached species or "unattached fraction," are single atoms of solid, charged, heavy metals (Po, Pb, Bi) that rapidly combine with other charged species in the atmosphere (e.g. H_2O, SO_2, NO_x) to form particles whose sizes are in the range of 0.5 to 5 nm. Defining the size and the magnitude of the unattached fraction is important because Rn progeny that reach the trachea, and are in the unattached size range, have a much higher probability of depositing on the surfaces of the bronchial airways than do particles whose sizes are more characteristic of ambient aerosols (50–500 nm) (54, 55). The unattached fraction of Rn progeny can therefore significantly and disproportionately affect the radiation doses to the conducting airways of the lung.

Hopke (53) recently reviewed the data on measurements of the unattached fractions in mine and indoor domestic environments, as well as the state of the art of instrumentation for measuring ultrafine particle size distributions as they relate to Rn progeny characterization. Because instruments for measuring size distributions down to 0.5 nm have only recently been developed, existing data are inadequate to confidently define the fraction of Rn progeny that are unattached under the different atmospheric conditions that can occur in mines and in homes. Nevertheless, based on current data, Hopke has concluded that: (*a*) unattached Rn progeny atoms are associated with ultrafine particles with sizes in the range of 0.5 to 5 nm. This variability in size is important because the rate of diffusion increases significantly with decreasing size within this range, and this will affect the deposition probability in the respiratory tract. Thus, Rn progeny cannot be characterized by a single value of either particle size or diffusion coefficient, thus complicating the deposition modeling and mandating new size measurements in the range of 0.5–500

nm (56–59). (*b*) In general, the unattached fraction in active working areas of uranium mines is about three times lower than that of a typical indoor domestic environment. However, the unattached fraction in both mines and homes is greatly influenced by the particle number concentration in the air. For particle number concentrations above 10^4 particles/cm^3, the unattached fraction can be less than 0.05, and it decreases with increasing particle concentration. The variability in measured values of the unattached fractions has led different authors to assume different averages and ranges for mines and homes (55, 60, 61). The range of unattached fractions is typically between 0.01 and 0.40. (*c*) The particle size distributions of Rn progeny in indoor environments are heavily influenced by human activities, e.g. cigarette smoking, cooking with gas flames, heating with kerosene fuel, etc (53).

In addition to particle-size distribution, potential α-energy concentration (PAEC), and unattached fraction, the degree of disequilibrium between the Rn progeny and the parent Rn in the air can also affect the dosimetry of inhaled Rn progeny. Under ideal (i.e. nonrealistic) conditions, all progeny resulting from the decay of each Rn atom would remain suspended in the atmosphere, and radioactive equilibrium would be achieved. However, several mechanisms act to remove the progeny from the air so that at any given time, fewer progeny are present than were created by decay. The variables that drive the particle-removal processes are more important in indoor than in outdoor environments, and include particle number concentration, ventilation rate, plateout rates onto surfaces, and the unattached fraction (31). Measured equilibrium factors (defined as the ratio of actual measured Rn progeny concentration to the equilibrium progeny concentration calculated from the amount of Rn present at the time of measurement) have tended to range between 0.3 and 0.8, with more values occurring at the lower end of the range. The UNSCEAR (31) has adopted an average value for indoor environments of 0.4, which is consistent with the value of 0.37 used by Jacobi (62).

The equilibrium factor is significant because Rn and Rn progeny concentrations in indoor environments are usually measured according to the amount of Rn present, i.e. progeny concentrations are not measured. Since it is well known that the important radiation dose to the respiratory tract is due to the progeny, then either an assumed or a measured value for the disequilibrium state of the daughters must be used to obtain an estimate of the actual radiation dose to the respiratory tract.

DOSIMETRY MODELS FOR INHALED RADON PROGENY

It is not possible to measure the α-radiation dose that is being delivered to the human respiratory tract, as a whole or in part, from inhaled Rn progeny.

Therefore, theoretical dosimetry models are used to relate atmospheric Rn progeny concentrations to a dose received by the respiratory tract, and ultimately to the incidence of biological effects. Many models have been developed over the past 30 years; in general, newer models are more complex, reflecting increased knowledge and sophistication of analytical and modeling techniques. To dissect the different sources of variability in dose estimates, it is helpful to divide the different dosimetry models into their component parts: (*a*) morphometry, (*b*) deposition, (*c*) clearance, and (*d*) integrated dosimetry models.

Morphometry Models

The structure of the respiratory tract is customarily divided into three regions: (*a*) the extrathoracic or head airway region, which includes the nasal airways, oral cavity, pharynx, and glottis; (*b*) the conducting airways, which include the larynx, trachea, bronchi and bronchioles to the level of the terminal bronchioles; and (*c*) the respiratory region, which includes the respiratory bronchioles, alveolar ducts, and alveoli. Morphometry models as applied to Rn progeny dosimetry have focused on the conducting airway region because most cancers that occur in miners are considered to be bronchogenic. Furthermore, the other regions of the respiratory tract are less amenable to geometric simplification than the conducting airways, which can be modeled as a series of bifurcating cylindrical tubes. This is particularly true for the nasal airways. The most commonly used morphometric models of the conducting airways are the Weibel symmetric dichotomous model (63), the Yeh-Schum "typical path" model (64), and the model of Phalen et al (65). James (60) has calculated bronchial airway doses using each of the above models, and found that the values were within a range of 30%, indicating that the selection of morphometric model does not appear to contribute significantly to the uncertainty in the calculation of dose to the conducting airways.

Deposition and Deposition Modeling

One of the most important components of any Rn progeny dosimetry model is the deposition model, and the parameter values used in the calculations. Because aerosol deposition is so important for any inhaled material, many human studies have been conducted in the past and their results summarized in numerous review articles (66–71). Most deposition studies used aerosols of relatively large particle size, (0.5–10 μm aerodynamic diameter (66, 72–75). Beyond this range of particle sizes, there are few data. Heyder et al (69) reported on aerosol deposition in people for sizes extending downward to 0.005 μm, but provided no information on the regional sites of deposition because measurements were only for the respiratory tract as a whole. The most important particle size ranges for inhaled radon progeny are 0.5–5 nm

for unattached progeny, and 0.05–0.5 μm for attached radon progeny in mines and homes.

Although dosimetry modeling in the past has emphasized the conducting airways, deposition data and models for each of the different respiratory compartments are needed. In part, such information is available for deposition of large-sized aerosols in the nasal and oral cavities (75–81), in the conducting airways (82–84), and in the respiratory region (69, 72, 84–87). Fewer studies have used particle sizes of interest to Rn progeny dosimetry, i.e. 0.001–0.5 μm (69, 88).

To obtain deposition data with better spatial resolution than can be obtained in nondestructive in vivo studies, several investigators have used physical replica models (casts) of either the head airways or the tracheobronchial tree (89–97). Data from these cast studies have provided additional information for contemporary deposition models. For example, models of the conducting airways beginning at the level of the larynx or trachea and extending distally for several airway generations have been used to determine velocity profiles and flow patterns (98, 99), which have then been used in developing theoretical fluid dynamical descriptions of the flows within the conducting airways. Others have determined that larger-sized aerosol particles that deposit primarily by impaction and sedimentation mechanisms, are found in significantly increased concentrations in the region of airway bifurcations, which could lead to increased radiation doses in those areas (91, 100–102). Without experimental data, it is not clear whether such heterogeneous deposition patterns in conducting airways will also occur with ultrafine aerosols.

Knowing the deposition pattern for radon progeny in the bronchial airways is particularly important because the bronchogenic cancers seen in the uranium miners were most common in the lobar and segmental bronchi. These locations have been calculated to have high local particle depositions, particularly for sizes in the range of the unattached fraction of radon progeny (54, 55). These calculations, which assumed mouth breathing, showed maximum deposition probability in the fourth generation, with the probability decreasing by more than two orders of magnitude by the twelfth airway generation, which corresponds anatomically to the mid-bronchiolar region. Thus, for these ultrafine aerosols, deposition was virtually complete in the bronchial tree with minimal penetration to the alveoli. Unfortunately, limited experimental data on radon progeny deposition exist (103–107), and the exposure atmospheres were not well characterized, particularly in terms of particle size distributions. Therefore, deposition model calculations have not yet been satisfactorily verified with experiments using Rn progeny aerosols.

Before 1980, aerosol deposition in the nasal airways received limited attention, particularly for the ultrafine particle sizes. This was due primarily to the lack of experimental data. However, recent studies by Cheng et al (108)

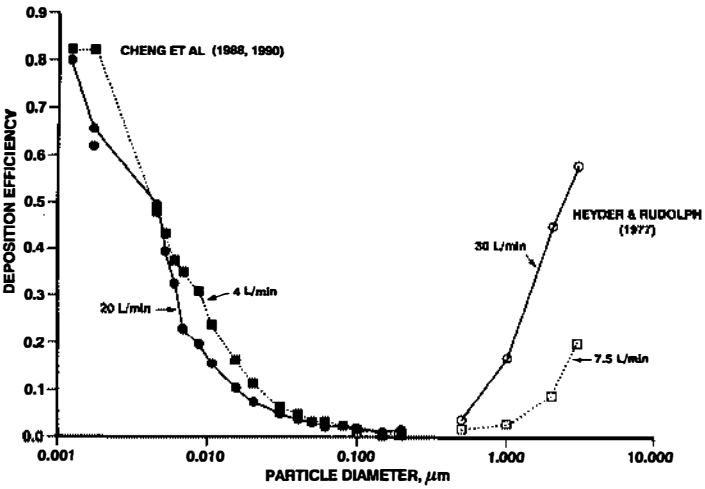


Figure 2 Deposition of aerosols of widely different sizes in human nasal airways. Data combine deposition measurements obtained in vivo and in casts.

and Yamada et al (109), using a nasal cast derived from a human cadaver, indicated that deposition of ultrafine aerosols in the nasal airways was much higher than previously assumed (Figure 2). According to their results, about 80 to 90% of 1- to 2-nm-sized unattached radon progeny would deposit in the nasal region, thus reducing bronchial deposition dramatically. More recently, Cheng et al determined the deposition of ultrafine aerosols in a human oral cast and found that the deposition efficiencies for inspiratory flow were essentially the same for nasal and oral passages, but somewhat less in the oral cast for expiratory flow (110). Thus, at 0.006 μm, inspiratory deposition in the oral cast was between 40 and 50%. Although data for smaller sizes more comparable to those of the unattached fraction of Rn progeny were not studied, 80–90% deposition for 0.001 μm-sized aerosols in the oral airways could be expected. However, the cast data need to be validated with deposition data obtained in vivo.

The breathing pattern and body size also influence the regional deposition pattern of aerosols for a given exposure to radon progeny. The apparent correlation between the lung tumor site in uranium miners and the calculated deposition site of radon progeny may apply only for specific conditions. Mouth breathing and ventilation rates typical of light work were assumed. These are probably reasonably good assumptions for men working in a mine. The use of mouth breathing and the fact that many of the miners were cigarette smokers, which itself results in upper airway injury and bronchogenic carcinoma, may have heavily influenced the response seen. However, the

exposure-dose-response relationships may be very different for nose breathing by people in domestic environments.

Clearance and Clearance Modeling

Clearance is a defense mechanism of the respiratory tract to remove inhaled deposited particles. Generally, clearance is classified into several categories: mucociliary clearance, extracellular dissolution, macrophage-mediated dissolution, and long-term clearance via lymphatics or conducting airways. It is generally thought that clearance of particles is independent of particle size, whereas dissolution of particles is size-dependent (111, 112). For radon progeny, especially the unattached progeny, the major deposition sites are in the head airways and tracheobronchial region. Therefore, their clearance rate would not be expected to be size-dependent. However, because of the short half-lives of Rn progeny, the initial deposition sites and the rate of mucus clearance in the nasal, tracheal, and bronchial airways will be determinants of the radiation dose. Several dosimetry models have incorporated clearance half-times for both head airways and for the bronchial region on a generation-by-generation basis (60, 113–116). Although there is agreement that clearance of particles from the ciliated epithelium of the nasal airways is very rapid, i.e. $\approx$ 10 minute half-time (117), there is no such agreement in the assumed mucous clearance rates in the different generations of the tracheobronchial tree. The reason is that mucus clearance rates in humans have mostly been measured in the trachea, not in the distal airways (118–121), and the values of bronchial clearance rates have depended on the structure and assumptions of the clearance model that relate primarily to how and where mucus is produced within the lung, as well as the appearance and disappearance of lung water. Harley calculated the effect of eliminating mucociliary clearance on the activity concentrations of Rn progeny in the fourth generation of the tracheobronchial tree, and found that the concentration of α-emitting progeny increased by only about 25% (61). However, another scenario in which clearance from the fourth generation was arrested but clearance from the more distal airways was not, yielded three- to fivefold increases in progeny concentrations (61). Thus, it was concluded that the effect of different mucus clearance rates was not large, provided that unusual patterns of impaired clearance were not present.

Dosimetry Models

Many mathematical dosimetry models have been developed specifically for Rn and Rn progeny dosimetry. Forty-eight such models were summarized in NCRP Report Number 78 (61) and others have subsequently been published (3, 31, 38, 60, 122–128). Historically, as knowledge has increased, the models have become increasingly complex and mathematically sophisticated.

Nevertheless, they still suffer from a lack of validating experimental data. Thus, much of the current debate relating to the extrapolation of risk values derived from miners to the general population centers on disagreements about dosimetry and dosimetry modeling. These disagreements deal not only with the most appropriate structure of the model, but also with the values of the parameters used in the calculations. A panel of the National Research Council, National Academy of Sciences, has recently addressed in detail the issue of the potential dosimetric differences between Rn progeny exposures in homes and mines (129).

In general, the relationship of exposure to dose is quantified in terms of a "dose conversion factor", given in units of mGy/WLM or rads/WLM. In comparing dose conversion factors from different dosimetry models, account must be taken of the assumptions and parameter values used in the model calculations. Historically, the reported dose conversion factors have ranged from 0.7 mGy/WLM (62) to 140 mGy/WLM (130), a factor of 200. For the more recent models, however, values appear to converge such that a more realistic range of dose conversion factors would be between 2 and 10 mGy/WLM (60). Only recently have dosimetry models calculated the dose conversion factors to take into account the differences between exposure of adult men in mines, and the general population in homes (38, 39, 60, 61, 129). The differences have in general been less than a factor of two.

Critical Cells at Risk

Identification of critical cells at risk in the respiratory epithelium is important from both dosimetric and biological points of view. Critical cells for radon progeny-induced lung cancer can be defined functionally as cells that are capable of: (*a*) being irradiated by inhaled deposited radon progeny; (*b*) proliferating; (*c*) differentiating into the types of cells found in lung tumors; and (*d*) being transformed into cells that can progress to neoplasia.

Epithelial cells lining the respiratory tract can be irradiated by inhaled radon progeny; however, because of the short range of alpha particles in tissue, the dose to particular cells will be critically sensitive to the depth of the cells within the epithelium and the location of the Rn progeny. Figure 3 depicts a cross-section of human bronchial epithelium, with the important cell types identified along with some cellular dimensions typical of normal humans. According to Gastineau et al, the median epithelial thicknesses were 80 $\pm$ 6 μm for the main bronchi, 50 $\pm$ 12 μm for the lobar bronchi, 50 $\pm$ 18 for the segmental bronchi, 20 $\pm$ 5 for the transitional bronchi, and 15 $\pm$ 5 for the bronchioles (131). As mentioned previously, the major contributors to the radiation dose are the alpha particles emitted by ^{218}Po and ^{214}Po, which have ranges in tissue of 48 and 71 μm, respectively (124). In the upper airways, the more basally located cells are predominantly out of range of the alpha

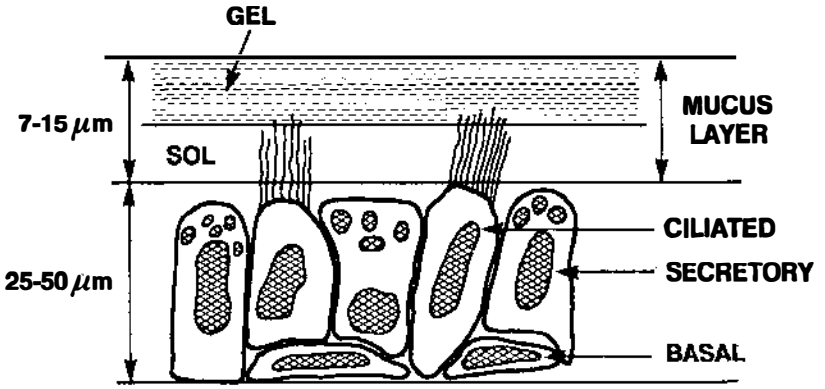


Figure 3 Schematic cross-section of human bronchial epithelium showing the different cell types of concern, and the different thicknesses of mucus and cells.

particles from ^{218}Po, but not so for those of ^{214}Po, assuming that the progeny are located throughout the mucous layer, which has been assumed to have thicknesses of 7 to 15 μm (124, 125). On the other hand, the secretory and ciliated cells are within range of the α particles from both Po isotopes regardless of the assumed distribution of Rn progeny within the epithelium or mucus. Therefore, the calculated α-radiation dose to the epithelium of the conducting airways will depend on the choice of critical cellular targets, as well as their sizes and locations within the epithelium.

The tissue specimens used by Gastineau et al were clinically normal (131). However, dramatic changes in the numbers of epithelial cells and the epithelial thickness can occur as a result of cigarette smoke exposure, which is typified by mucous cell hyperplasia (132). Additionally, the data described above are for adult lungs. During early postnatal development, the epithelial lining in the upper airways is thinner (133), which would result in a different distribution of α-radiation dose and allow the entire basal cell population to be irradiated. The cells lining the bronchioles and the lung parenchyma are well within range of the α emissions from Rn progeny. As yet, no attempts have been made to incorporate different epithelial thicknesses, be they due to developmental or pathological causes, into dosimetry models.

In the first five generations of the human airways, where Rn-progeny-induced (and cigarette-smoke-induced) tumors occur, the major epithelial cell types are the basal, secretory (mucus/serous), and ciliated cells. The ciliated cells are terminally differentiated, play a minor role in repair and replacement in the tracheobronchial lining, and are apparently incapable of division (134).

Relatively little is known of the proliferative and differentiation potential of the basal and secretory cells of the human respiratory epithelium. Much of our

knowledge in this area has come from studies with animals. Historically, the basal cell has been considered to be the important progenitor cell in the epithelium of the upper airways, mainly by analogy with the undifferentiated basal progenitor cells found in other types of mammalian epithelium such as skin, intestinal tract, and urinary bladder. As a consequence, many existing dosimetry models have calculated α-radiation doses to these basal cells (37, 38, 55, 124, 125). Light microscopic studies using tritiated thymidine to label cells in S phase have shown that basal cells differentiate into both secretory and ciliated cells (135, 136). Recent studies in which highly purified populations of basal cells obtained from rabbit tracheas were inoculated into denuded tracheas transplanted into nude mice showed that the basal cells were capable of regenerating a normal-looking fully differentiated epithelium (135). These data suggested that the basal cell had progenitorial capacity, and could be considered a stem cell for the tracheal epithelium (136).

On the other hand, a significant body of data suggest that tracheobronchial secretory cells may also have proliferative and progenitorial capacities. In the hamster trachea, denuding injury results in a proliferative response in the surrounding secretory cells followed by reestablishment of the epithelium and the appearance of preciliated cells (137). Evidence from electronmicroscopic examination of cells in squamous metaplastic lesions, which are frequently considered to be expressions of aberrant basal cell division, showed that the lesions arose from keratinization of secretory cells, thus implying that the secretory cell is not terminally differentiated (134). Recent studies by Johnson et al (138) in which basal and secretory cell populations obtained from rat tracheas were purified using flow cytometry and inoculated into denuded rat tracheas for repopulation have indicated that the secretory cells accounted for 86% of the cycling cells in vivo and 85% of the cells capable of proliferation in vitro. Inoculation of a 92% pure population of secretory cells into a denuded rat trachea resulted in a reestablished epithelial lining consisting of basal, secretory, and ciliated cells. On the other hand, inoculation of a 95% pure population of basal cells resulted in a lining composed only of basal and ciliated cells (139).

The question of the critical cells at risk for the production of cancer by α irradiation from Rn progeny has clearly not been resolved. This issue is crucial for understanding the mechanisms of initiation, promotion, and progression of radiation-induced cancer. However, from a dosimetric point of view, the problem is less complicated. James has shown that the α-radiation dose calculated to the entire thickness of epithelial cells, which contains both basal and secretory cells, is about twice as large as the dose calculated solely to the basal cell population (60). Given current knowledge, it would seem prudent to base the dose calculation either on the whole epithelial thickness, or to calculate doses separately to the secretory and basal cell populations.

Epidemiological Studies

Excess pulmonary disease in miners of uranium-rich ores has been recognized for centuries (8); the excess of bronchogenic cancer was attributed to the high radiation levels found in the mines (140, 141). Radon levels measured in US uranium mines in 1950 were similar to those reported for mines in the Erz mountain area of central Europe (142). The first epidemiological study of U miners was begun in 1954 with the identification of a study group of 3,366 white and 780 nonwhite workers who had a minimum of one month of underground uranium mining experience (12). Until recently, this prospective study, which is still in progress, provided one of the few data bases for estimating Rn-progeny-induced lung cancer risks. Subsequently, other epidemiological studies of Colorado plateau miners (143, 144) and uranium mining populations in Canada (15, 18, 145, 146), Czechoslovakia (17), and France (147) have been published. In addition, epidemiological studies of nonuranium miner populations have also been reported (19–25, 27, 148–153). These latter populations involved mining of iron ore, magnetite, fluorospar, zinc/lead, tin, niobium, and other metal ores.

The epidemiologic studies of underground miners have clearly demonstrated that the risk of lung cancer increases in groups of miners who receive cumulative lifetime exposures above 100 WLM, and that the excess risk increases with cumulative exposure (17, 37, 39, 143, 153–155). Several authors have calculated risk factors for Rn-progeny-induced lung cancer from either single populations or for several combined populations (15, 21, 37–39, 145, 156–160). Estimates of lifetime lung cancer risk in the different mining populations ranged from 1×10^{-4} to 7×10^{-4} per cumulative WLM of exposure. Despite large differences among the mining populations in age distribution, followup period, smoking history (or lack thereof), and uncertainties in exposure estimates, and the modeling approaches taken by different investigators, the risks are surprisingly similar among the studies.

As described previously, the exposure of miner populations to Rn progeny and exposures of the general population in domestic indoor environments differ significantly. These differences lend uncertainty to the extrapolation of the risk factors derived exclusively from the miner studies. Additionally, the variability in the data from the largest miner studies also adds to the uncertainties (this latter variability is the main reason why so many different risk models can be said to "fit the data"). Since the quality of the miner data is unlikely to improve significantly (except for completion of followup of the surviving fraction of miners), it has become most important to evaluate the risk from Rn-progeny exposure in indoor environments through epidemiological study of populations of people exposed at different Rn-progeny levels within their homes. However, such epidemiologic evidence has been much more difficult to obtain. Samet (155) has recently reviewed the principal

published reports that include both descriptive studies and epidemiologic studies of domestic exposure to radon progeny and the onset of lung cancer. Of the 11 descriptive studies cited, six showed positive correlations between exposure to radon and the incidence of or mortality from lung cancer. Measures of exposure included the presence or absence of uranium-rich phosphate deposits (161), ^{226}Ra levels in drinking water (162), estimated background γ radiation (assumed to correlate with radon levels (163)), county averages for Rn in water (164) and by county (165, 166). On the other hand, four studies showed no correlation of lung cancer mortality with either mean WLM estimates for 18 Canadian cities (167), soil geologic features (168, 169), or high or low background areas (170), and one study showed lung cancer mortality to be inversely associated with county average radon levels (171). However, Samet concluded that the evidence from the descriptive studies was not conclusive because neither exposures to individuals nor other agents such as cigarette smoke were considered.

The results from more statistically valid case-control and cohort studies were also reviewed, with similarly mixed results. Some studies showed statistically significant increases in the relative risk for lung cancer associated with exposure, others did not. Availability of information on actual radon progeny concentrations, cigarette smoking history, or lifetime residence history differed among the studies. Samet attributed the mixed study outcomes to small sample sizes and the use of surrogates of exposure in lieu of actual Rn or Rn progeny measurements.

In a recent study of indoor Rn and lung cancer in China, Blot and colleagues (172) made a population-based, case-control study of a relatively large population of women in northern China (308 cases of newly diagnosed lung cancer, 356 controls). A unique feature of this study was that the researchers made one-year cumulative Rn measurements in the homes of each of the 664 study subjects (median residence time in the homes was 24 years). The Rn levels were not found to be higher in the homes of the women with lung cancer compared to controls (median level = 85 Bq/m^3), nor did lung cancer incidence increase with increasing levels of Rn. Their results, therefore, do not support the risk factors derived from miner populations. Obviously, more carefully controlled studies such as this are needed, where actual measurements of individual Rn progeny levels are made.

Animal Studies

Contemporary studies of the effect of Rn-progeny-containing aerosols in producing lung cancer in animals have provided significant data that are useful in supplementing the epidemiological results from miner populations. In particular, because of the ability to control such variables as unattached fraction, equilibrium factor, particle size, and Rn progeny concentration, the

effects of these potential dose-modifying factors can be evaluated. Most recent experimental animal data have emerged from studies conducted in rats at the Centre d'Étude Nucléaire in France and from studies in rats, dogs, and hamsters at Pacific Northwest Laboratories (PNL), USA. Several reviews of the results of the animal studies have been published (36, 37, 39, 173–175).

Chmelevsky et al (176) and Gray et al (177) have performed dose-response analyses on the composite of 22 of the French studies, in which rats were exposed by inhalation to different exposure levels of Rn progeny. Both investigators used statistical methods that corrected for competing causes of death, and allowed for the occurrence of nonlethal tumors, which was a common occurrence in these studies. Rats exposed to ≥6000 WLM had decreased lifespan. When adjusted for life-shortening, the analyses indicated that the excess risk for developing lung tumors was linearly related to the exposure dose down to 65 WLM. This point is important since dose-response relationships that have been uncorrected for lifespan shortening yield non-linear relationships with increasing incidence per unit of exposure for decreasing cumulative exposure level (39). Gray et al also determined that significant dose-response relationships existed for each class of pulmonary lesion analyzed, i.e. malignant tumor, benign and/or malignant tumor, tumor and/or preneoplastic lesion, and any cellular abnormality or lesion (177).

Recently Gilbert used statistical modeling methods that accounted for competing risks and allowed for the occurrence of lung tumors as incidental findings, and analyzed the data from 12 experimental groups of rats from the PNL rat studies (178). Six of the groups were exposed at 100 WLM per day to cumulative exposures of 300 to 10,000 WLM, five of the groups were exposed at 50 WLM per week to 300–5000 cumulative WLM, and one group was exposed at 5 WLM per wk to 300 cumulative WLM. As with the analyses of Gray et al for the French rat studies, Gilbert determined that the attenuation of risk at very high cumulative exposures was not found when competing risks were accounted for. This was true whether the tumors were considered to be incidental or fatal. The quantitative risk coefficient for the rats, 300 per 10^6 rats per WLM was similar to that found in analyses of miner populations, e.g. 350 per 10^6 persons per WLM (39). However, it is probably more appropriate to compare the risk for rats to the estimate for nonsmoking people, i.e. 140 for male nonsmokers (39) or 130 per 10^6 persons per WLM (37). Gilbert also pointed out that the apparent increased risk seen at lower dose rates could possibly have been an effect of time since exposure or time since cessation of exposure, because more protracted exposures are necessary for the lower dose-rate groups to obtain similar cumulative WLM exposures.

Other findings from the animal studies are also notable. The spectrum of tumor types among the 500 rat tumors from the French studies was similar to that of the human lung tumors, with the exception of a lack of small cell

carcinoma in the rats (179). The French studies included 56% epidermoid, 15% adenocarcinoma, 30% bronchioloalveolar plus alveolar, and 2% giant cell tumors. The types of tumors seen in the PNL rat studies were said to be similar to those in the French studies (174). Increased age at beginning of exposure appears to shorten the latent period for tumor development (39). This was also pointed out by Archer et al (13) in their analysis of the Colorado plateau miner data, and is reflected in the time-dependent structure of both the ICRP and BEIR IV relative risk models. Exposure to nonradioactive $Ce(OH)_3$ prior to Rn progeny exposure shortened the latent period for tumor development by 2–3 months in rats; however, uranium ore dust appeared to have little influence on the carcinogenic process (180). Similarly, coexposure of rats to Rn plus either uranium ore dust or diesel exhaust increased the number of preneoplastic lesions but did not change the incidence of lung cancers in the PNL studies (39). Extrapulmonary tumors, principally in the nasal airways and the larynx were reported in the PNL studies, but not in the French studies (174). Extrapulmonary tumors were also seen in dogs exposed to Rn-progeny aerosols. The frequency of occurrence of these tumors in rats increased with increasing unattached fraction. This would appear logical because the ultrafine aerosols deposit with very high efficiency in the nasal airways of rats (181). Lung tumor risk in the PNL rat studies increased with increasing unattached fraction of Rn progeny and with increasing disequilibrium (174). However, these conclusions appear to have been based on analysis of crude incidence rates, and could be subject to the same biases that were pointed out regarding dose rate effects by Gray et al and Gilbert (177, 178).

The Issue of Smoking and Radon Progeny Exposure

The lung tumors associated with underground uranium miners occur mainly within the first five divisions of the bronchial tree (182). The issue of the roles of smoking and Rn progeny exposure in the induction of lung cancer are intimately linked when considering the miner populations, as most of the miners who have been studied were smokers. Doll & Peto (182) estimated that 88% of the lung cancer deaths in the United States in 1977 were due to cigarette smoking. Therefore, detection of increased risks from other agents such as Rn progeny requires control for the potential confounding effects of cigarette smoking (183). Steinhausler (154) has summarized the known smoking experience reported in the different mining populations: ≈70% smokers for the Colorado plateau miners, 60–67% for Swedish hard-rock miners, 80% in the Newfoundland fluorospar miners, 85% for the Norwegian niobium miners, 70% for the Czechoslovakian and French miners (38), and 50–60% of the Canadian miners (38). What has also become clear is that the large majority of lung cancers in the miner populations occurred in smokers. For example, 94% of lung cancers in the Colorado plateau miners were in

smokers (156) and 96% of a small group of lung cancer cases from the Czech miners were smokers (184). On the other hand, it is also clear that Rn-progeny exposure in the absence of cigarette smoking also results in increased incidence of lung cancer (17, 21, 144, 185, 186).

Several investigators have analyzed the epidemiological data from different populations of miners exposed to Rn progeny who also were smokers. To date, the epidemiological evidence has not led to a firm conclusion concerning the interaction between exposure to Rn progeny and smoking. However, at this point, most analyses tend to favor a multiplicative or synergistic interaction model (12, 13, 20, 36, 38, 39, 148, 157, 162, 187–189); a minority of the studies favor either additive or submultiplicative models (21, 36, 39, 158).

Several animal studies have employed exposures to Rn progeny and to cigarette smoke. However, the results have done little to clarify our understanding of the interactions between these two agents. Chameaud et al (179) described studies in which rats were exposed to cigarette smoke either before or after exposure to Rn progeny. When cigarette smoke exposure preceded Rn exposure, there was no increase in tumor yield over Rn-progeny exposure alone. However, when cigarette smoke exposure followed the Rn-progeny exposure, there was a significant synergistic increase in the number of lung tumors. At a cumulative exposure of 500 WLM, 7% of the animals had lung cancer, whereas after smoke exposure, 25% had tumors; at 4000 WLM, 34% had tumors in the Rn only group, 68% in the Rn plus smoke group (179). In the PNL dog studies, lung tumor incidence decreased relative to tumor incidences for Rn progeny alone when the dogs were exposed to Rn progeny and cigarette smoke separately but on the same day (190). This effect was attributed to a protective effect of mucous hypersecretion within the bronchial airways from the cigarette exposures that reduced the α-radiation dose to the sensitive epithelial cells by shielding of the mucous layer (190).

That these animal studies have not clarified the interactions between Rn progeny and cigarette smoke is not surprising since currently no good animal model exists for the bronchogenic carcinoma induced in humans from inhaled tobacco smoke. Although smoking-induced tumors have been reported in mice, rats, and dogs, the tumors have been primarily associated with the parenchymal lung, with laryngeal tumors also occurring (191). The evidence from the French and other cofactor studies (191) seems to indicate that the primary role of cigarette smoke in lung cancer in animals is as a promoter. In people, by contrast, exposure to cigarette smoke alone is considered to be sufficient to cause lung cancer (192). Thus, we should not expect to be able to dissect the interactions between smoking and other cofactors such as Rn progeny until an adequate animal model has been defined. The lack of cigarette-smoke-induced bronchogenic carcinoma in animals might reflect

differences in regional dosimetry and total dose between humans and laboratory animals (J. L. Mauderly, personal communication).

Summary Remarks and Research Needs for Rn-Progeny-Induced Lung Cancer

For most people, the inhalation of Rn and Rn progeny constitutes the major source of exposure to ionizing radiation, approximately half of the yearly total when expressed on an effective dose basis. The numerous epidemiological studies of both uranium and nonuranium miners have shown conclusively that exposure to high levels of Rn progeny results in a substantially increased risk for lung cancer, and that there is an exposure-response relationship, i.e. increased cumulative exposure yields increased risk of lung cancer. It is also reasonably evident that exposure to Rn progeny and cigarette smoke results in a synergistic interaction so that the increased risk from the combination is a multiple of the individual risks. This conclusion must be viewed with some caution at this point, however, because the different epidemiological studies have been inconsistent in demonstrating synergism, nor have the follow-ups of the study populations been completed. Assuming a multiplicative model, however, leads to the conclusion that smokers are at about ten times the risk as nonsmokers for acquiring lung cancer per unit exposure to Rn progeny.

Measurement of Rn and Rn progeny concentrations in domestic atmospheres have shown large variabilities in concentrations, attributed mainly to different rates of influx of Rn from the underlying soil. Many national and multinational organizations have concluded that exposure to high levels of Rn and Rn progeny is undesirable and associated with unacceptable risk, and have recommended limits for concentrations of Rn deemed to be acceptable in indoor environments (30). Current values for Rn concentration limits vary from 150 to 800 Bq/m^3, but there appears to be a trend developing such that future action levels will center at 400 Bq/m^3 for existing houses and 200 Bq/m^3 for new houses (30). In the United States, the long-term goal of Rn risk reduction is that the concentration of Rn within homes should be no greater than the Rn concentrations outdoors. It is not clear that implementation of such a policy, costing an estimated $1 trillion (193), would be cost-effective in decreasing the lung cancer incidence (calculated to be $3 million per lung cancer averted (193)). Far more effective in reducing lung cancer risk would be the elimination of cigarette smoking, an option that has been suggested previously (153, 193). This would be true whether the Rn-smoking interaction were to be described by a multiplicative or a submultiplicative model.

The issue of the health risks to the general population associated with exposure to Rn progeny in indoor environments is timely, important, and as yet incompletely answered. Incomplete data and lack of understanding of the roles of the many confounding factors associated with Rn progeny exposures

in mine and home environments offer opportunities for new research designed to address these unresolved issues. By analogy with the risk assessment model for inhaled toxicants, described above, the research issues and future research needs can be grouped according to the different components of an integrated risk assessment.

Atmosphere

1. More complete measurements of the Rn progeny particle-size distributions are needed, particularly as a function of type of indoor environment, and the type and level of aerosol-producing activity occurring within. Better understanding of the mechanisms of particle removal dynamics from the atmosphere will then permit better mathematical models to be developed and used to characterize different types of indoor or mining environments.
2. An estimated 70,000 homes in the United States have average Rn levels that exceed 800 Bq/m^3. Long-term exposure at this level could result in an exposure rate of 4 WLM/y, which is the regulatory limit of exposure for underground miners. This would likely result in an unacceptably high level of risk of lung cancer, particularly for smokers. These homes should be identified, and mitigation used to reduce exposure levels.
3. Strategies for obtaining better mapping of indoor Rn and progeny levels for a large numbers of homes are needed. Although Rn levels could feasibly be measured in every home in the United States, other approaches have been proposed to identify areas with homes with potentially high Rn concentrations, by using existing geological information in combination with measurements in small samples of houses in a particular region (193). Long-term (e.g. yearly integrated) measurements should be emphasized to provide the most useful information. Such mapping of more local or individual Rn levels will also provide a better dosimetric underpinning for future epidemiological studies.

Exposure

1. Recent studies using physical replicas of nasal and oral airways have pointed out the need for improved understanding of the regional deposition of Rn-progeny-containing aerosols with particle sizes in the range of 0.5–500 nm. These data can be obtained in vivo using surrogates for Rn-progeny-containing aerosols in both humans and experimental animals. Other data for deposition of ultrafine aerosols in conducting airways are also needed to validate existing theoretical deposition models.
2. Better age-specific and gender-specific morphometric measurements are needed to be able to adapt existing models. This can be done using a combination of post-mortem casting techniques and noninvasive measure-

ment techniques such as magnetic resonance imaging or computerized tomography (194).

3. More extensive interspecies modeling of aerosol deposition will better relate results of experimental animal studies with epidemiological data, in which distribution of pathological effects are often different. It is important to understand whether the observed differences are due to differences in dose distribution, or differences in biological response.

Dose

1. Current dosimetry models for inhaled Rn progeny are tending to predict radiation dose distributions that are more and more consistent with each other. Comparison of radiation dose distributions for mine and home exposure scenarios are also indicating that the differences in doses may not be large, i.e. within a factor of two to three. However, all of the modeling approaches suffer from the paucity of validating data, particularly for data obtained at the regional level. Recently, a "biodosimetric" or "deductive dosimetric" approach has been proposed in which the biological responses of isolated cell populations that have been previously exposed to known levels of Rn progeny in vivo are compared to the responses obtained from similar populations of cells that are irradiated in vitro using plated α sources, where the α-radiation dose can be measured or calculated accurately. By comparing exposure levels and α-radiation doses that produce equivalent biological effects, a relationship between exposure level and radiation dose (or dose conversion factor) can be derived experimentally, and ultimately compared with predictions of the dosimetry models. This approach has several attractive features, in that it employs cultures of primary epithelial cells that can be isolated from different portions of the respiratory tract; the cells can also be sorted by flow cytometry into purified populations of different cell types to study differences in biological response to α-irradiation. The response endpoints now include cytotoxicity and transformation (195).
2. To date, all dosimetry models have utilized morphologic measurements from normal individuals. However, many respiratory diseases can alter the morphology of the airway epithelium, resulting in dysplastic or metaplastic changes that will certainly affect the α-radiation dose distribution. Such cellular changes may also alter the biological response of those cells to radiation. Thus, information on the dosimetry of altered airways is needed.

Response

1. One of the most important remaining issues to apply risk factors derived from the epidemiological data of miner populations to heterogeneous

populations of men, women, and children being exposed to Rn progeny in their homes is to determine the relative importance of Rn-progeny exposure, cigarette smoke, inhalation of metal and ore dust, and the presence of nonneoplastic disease in the multistage process of carcinogenesis. This is an exceedingly complex issue because of our limited understanding of the mechanisms of carcinogenesis. Nevertheless, experimental or epidemiological studies need to be designed that will provide new data and insights into the relative roles of the different cofactors in the production of lung cancer.

2. The question of the inverse dose-rate effect, i.e. that exposure to lower levels of Rn progeny results in higher risk factors per unit of exposure, remains to be resolved. Results of both epidemiological studies and experimental animal studies have been interpreted both in support of and conflicting with such an effect. Sometimes, different analyses applied to the same data bases have given conflicting conclusions. This issue needs resolution if the epidemiological data, in general obtained under high-dose-rate, limited exposure-period conditions, are to be applied to low-dose-rate, lifetime-exposure conditions in homes.
3. To contribute to our understanding of the mechanisms of α-radiation-induced cancer, we need to understand the biological consequences of irradiation of different epithelial cell types in terms of their ability to be transformed in the multistep process of carcinogenesis. Although this information may not contribute directly to improvement of risk assessment, it will provide a better radiobiological basis on which to compare results from these irradiated populations to others who have received irradiation by other means, e.g. the Japanese atom bomb survivors, persons injected with the radioactive X-ray contrast agent Thorotrast, patients treated with the α-emitter ^{224}Ra.

Risk

1. Carefully designed and executed epidemiological studies of indoor Rn-exposed persons need to be conducted on a larger scale. The studies should be designed not only to ascertain the association of radon exposure with lung cancer, but also to measure quantitatively the risk of lung cancer as it relates to the role of gender, age at exposure, temporal pattern of exposure, the combined effect of Rn progeny and cigarette smoking, and the risk to nonsmokers. This latter point is of particular importance. Coordination among scientists conducting such studies would allow results from the different studies to be pooled and thus increase the statistical power of the analyses (196, 197).

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