

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of radon. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Radon (Rn) is an inert noble gas that does not interact chemically with other elements. All of the isotopes of radon are radioactive and evaluation of the adverse health effects due to exposure to radon requires additional consideration of the effects of radiation. Radioactive elements are those that undergo spontaneous transformation (decay) in which energy is released (emitted) either in the form of particles, such as alpha and beta particles, or photons, such as gamma or x-rays. This disintegration, or decay, results in the formation of new elements, some of which may themselves be radioactive, in which case, they will also decay. The process continues until a stable (nonradioactive) state is reached. The isotopes of radon encountered in nature (^{219}Rn , ^{220}Rn , and ^{222}Rn) are part of long decay chains starting with isotopes of uranium (U) or thorium (Th), more precisely ^{235}U , ^{232}Th , and ^{238}U , respectively, and ending with stable lead (Pb). The intermediates between radon and stable lead are termed radon daughters or radon progeny (see Chapter 4, Figures 4-1, 4-2, and 4-3 for radioactive decay schemes of ^{235}U , ^{232}Th , and ^{238}U , respectively). The isotope ^{222}Rn is a direct decay product of radium-226 (^{226}Ra), which is part of the decay series that begins with uranium-238 (^{238}U). Thorium-230 and -234 (^{230}Th and ^{234}Th) are also part of this decay series. Other isotopes of radon, such as ^{219}Rn and ^{220}Rn , are formed in other radioactive decay series. However, ^{219}Rn usually is not considered in the evaluation of radon-induced health effects because it is not abundant in the environment (^{219}Rn is part of the decay chain of ^{235}U , a relatively rare isotope) and has an extremely short half-life (4 seconds). The isotope ^{220}Rn has usually not been considered when evaluating radon-related health effects, although many recent assessments have attempted to include measurements of ^{220}Rn as well as ^{222}Rn . While the average rate of production of ^{220}Rn is about the same as ^{222}Rn , the amount of ^{220}Rn entering the environment is much less than that of ^{222}Rn because ^{220}Rn is a noble gas with a short half-life (56 seconds). As a noble gas, it diffuses slowly from the ground but decays so rapidly into polonium (a particle that bonds with the soil) that most radon does not reach the atmosphere. The soil characteristics that enhance or retard radon migration from the

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soil indirectly affect air concentrations of radon and radon progeny. All discussions of radon in the text refer to ^{222}Rn unless otherwise indicated.

The decay rate or activity of radioactive elements has traditionally been specified in curies (Ci). The activity defines the number of radioactive transformations (disintegrations) of a radionuclide over unit time. The curie is the amount of radioactive material in which 37 billion disintegrations (decay events) occur each second (3.7×10^{10} transformations per second). In discussing radon, a smaller unit, the picocurie (pCi), is used, where $1 \text{ pCi} = 1 \times 10^{-12} \text{ Ci}$. In international usage, the S.I. unit (the International System of Units) for activity is the becquerel (Bq), which is the amount of material in which one atom disintegrates each second (1 Bq is approximately 27 pCi). The activity concentration of radon or any radionuclide in air is typically expressed in units of pCi/L or Bq/m³ of air. One pCi/L is equivalent to 37 Bq/m³. The activity concentration is typically a description of the concentration of radioactive material in air or water. The product of concentration and exposure time equals exposure; models are used to estimate a radiation dose to tissue from exposure. Since the isotopes continue to decay for some time, and some excretion occurs, the term dose refers specifically to the amount of radiant energy absorbed per mass in a particular tissue or organ and is expressed in rad (or gray).

As radon and its progeny decay, they cumulatively emit alpha and beta particles as well as gamma- and x-rays. The health hazard from radon does not come primarily from radon itself, but rather from its radioactive progeny (see Chapter 4 for more information on the chemical and physical properties of radon). When an atom of radium transforms to radon, the alpha particle it emits slows down by the attraction of nearby electrons until it captures two electrons and becomes a stable atom of helium (He). The transformed radon and subsequent decay product atoms are charged and tend to attach to aerosol particles. Radon progeny are similarly charged, readily aggregate, form clusters, and attach to dust particles in air. The main health problems arise when primarily those radon progeny that are attached to dust particles (termed the attached fraction) are inhaled, deposit in the airway (particularly the tracheobronchial tree), and irradiate nearby cells repetitively with alpha particles as each atom transforms through the decay chain. These alpha particles can deliver a large localized radiation dose. The attached fraction is much higher in homes with smokers relative to those with nonsmokers, and in dusty mines relative to those that are well ventilated. Exposures to radon gas are accompanied by exposure to radon progeny, although the exact mix of radon and progeny are determined by several physical-chemical and environmental factors. In this toxicological profile, unless indicated otherwise, *exposure to radon* refers to exposure to the mixture of radon and progeny.

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Because it is not feasible to measure the activities of individual radon progeny in the environment and while they decay inside the body, a unit termed the “Working Level (WL)” is used for the purpose of quantifying the cumulative radiation dose from inhaled radon progeny, which may not be in secular equilibrium. The WL unit is a measure of the amount of alpha radiation emitted from the short-lived progeny of radon. As applied to exposures to ^{222}Rn , this encompasses the decay series, $^{222}\text{Rn}(\alpha) \rightarrow ^{218}\text{Po}(\alpha) \rightarrow ^{214}\text{Pb} \rightarrow ^{214}\text{Bi} \rightarrow ^{214}\text{Po}(\alpha) \rightarrow ^{210}\text{Pb}$, and represents any combination of the short-lived progeny of radon. Working Level (WL) means the concentration of short-lived radon progeny in 1 L of air that will release 1.3×10^5 million electron volts (MeV) of alpha energy during decay. One WL is equivalent to the potential alpha energy of 2.08×10^{-5} joules in 1 cubic meter of air (J/m^3).

To convert between units of ^{222}Rn concentration (pCi/m^3 or Bq/m^3) and the potential alpha energy that can be released by its progeny as they fully decay (WL or J/m^3), the equilibrium between radon gas and its progeny at the time of exposure must be known or assumed (see Chapter 10 for conversion formula). When radon is in secular equilibrium with its progeny (i.e., when each of the short-lived radon progeny is present at the same activity concentration in air as ^{222}Rn), each pCi of radon in air will give rise to (almost precisely) 0.01WL (EPA 2003). By definition, 1 WL is equal to 100 pCi of radon gas. However, when removal processes other than radioactive decay are operative, such as with room air ventilation or air filtration, the concentration of short-lived progeny will be less than the equilibrium amount. In such cases, an equilibrium factor (F) is applied. The National Research Council Committee on Health Risks of Exposure to Radon (BEIR VI) assumes 40% equilibrium ($F=0.4$) between radon and radon progeny in the home (NAS 1999a), in which case, 1 pCi/L ($37 \text{ Bq}/\text{m}^3$) of ^{222}Rn in the air is approximately equivalent to 0.004 WL.

The unit of measurement used to describe cumulative human exposure to radon progeny in mines is the Working Level Month (WLM). It is the product of the average concentration in WL and the exposure time in months. One WLM is defined as exposure at a concentration of 1 WL for a period of 1 working month (WM). A working month is assumed to be 170 hours. The S.I. unit for WLM is $\text{J}\cdot\text{hour}/\text{m}^3$; $1 \text{ WLM} = 3.6 \times 10^{-3} \text{ J}\cdot\text{hours}/\text{m}^3$.

Measurements in WLM can be made using special equipment that measures the total alpha emission of short-lived radon progeny. However, measurements in homes are typically made for radon gas and are expressed in Bq/m^3 or pCi/L . To convert from residential exposures expressed in pCi/L , it is considered that 70% of a person's time is spent indoors and that 1 pCi/L of radon in the indoor air is equivalent to

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0.004 WL of radon progeny (EPA 2003; NAS 1999a). These conditions result in the following relationship:

$$1 \text{ pCi/L} \times 0.004 \text{ WL/pCi/L} \times 0.7 \times (8,760 \text{ hours/WL-year} \div 170 \text{ hours/WL-M}) = 0.144 \text{ WLM/year}$$

Because 1 pCi/L is equivalent to 37 Bq/m³, a residential exposure scenario using equivalent assumptions to those described above results in the same cumulative exposure to radon progeny (0.144 WLM/year).

As discussed in detail in Section 3.2.1 (Inhalation Exposure), lung cancer is the toxicity concern following long-term exposure to radon and radon progeny. The high-energy alpha emissions from radon progeny, deposited predominantly in the tracheobronchial tree, and to a lesser extent in the lung, are the major source of toxicity concern. As shown in Figure 4-1, the radiological half-life for radon (²²²Rn) is 3.8 days. The radioactive decay of radon to ²¹⁸Po (radiological half-life=3.05 minutes) is accompanied by the release of high-energy (5.5 MeV) alpha particles; decay of ²¹⁸Po to lead-214 (²¹⁴Pb; radiological half-life=26.8 minutes) also releases high-energy (6.0 MeV) alpha particles. Subsequent radioactive decay to bismuth-214 (²¹⁴Bi; radiological half-life=19.7 minutes) and ²¹⁴Po involve release of beta and gamma radiation, which are of sufficiently low energy and long range as to be considered of little relative toxicity concern to nearby cells. The decay of ²¹⁴Po via release of high-energy (7.69 MeV) alpha particles occurs so rapidly (radiological half-life=1.6x10⁻⁴ seconds) that, in radiation dose modeling, these alpha emissions are generally attributed to ²¹⁴Bi decay (i.e., the rate of decay of ²¹⁴Bi is essentially equal to the rate of formation of ²¹⁰Pb due to the essentially instantaneous decay of ²¹⁴Po from ²¹⁴Bi). The subsequently-formed radioactive radon progeny (²¹⁰Pb, ²¹⁰Bi, and ²¹⁰Po in respective order of decay) are not considered to make significant contributions to respiratory tract toxicity (relative to the short-lived progeny). This is, in large part, because the radiological half-life associated with the decay of ²¹⁰Pb is 22.2 years, which is sufficiently long that biological clearance mechanisms limit the radiation dose attributed to it and the other progeny. Therefore, the radon progeny of primary toxicity concern are ²¹⁸Po and ²¹⁴Po (due to the rapid decay of these alpha emitters, especially when part of the attached fraction).

3.2 DISCUSSION OF HEALTH EFFECTS OF RADON BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive,

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developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

ATSDR Toxicological Profiles typically include tables and figures for each route and duration in which levels of significant effects (LSEs) are presented. Points in the figures show no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) and reflect the actual doses (levels of exposure) used in each study for which adequate information is available regarding exposure level and a particular effect. LOAELs are classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear.

The December 1990 ATSDR Toxicological Profile for Radon included an LSE table and figure for exposure via the inhalation route in which levels of significant exposure were presented for noncancer effects in radon-exposed animals and cancer effect levels (CELs) were presented for lung cancer in humans exposed in the workplace, with the exception of one study of residential exposure. However, the LSE table and figure in the 1990 version of the Toxicological Profile for Radon were not retained in this update Toxicological Profile for Radon for the following reasons:

- LSEs for noncancer end points in the animal studies occurred at exposure levels that were several orders of magnitude higher than exposure levels expected to be of toxicological consequence in humans and are thus not reliable indicators of expected LSEs for noncancer end points in humans.
- Most occupational and residential studies of cancer end points (mainly lung cancer) include uncertain estimations of historical exposure levels for radon and radon progeny, and occupational studies are limited by confounding exposure to other substances including known human carcinogens.
- Assessment of individual epidemiological studies leads to uncertainty regarding human health effects associated with exposure to radon and radon progeny because individual studies may provide conflicting results.
- Recent emphasis has focused on pooled results from multiple human studies to provide more comprehensive evaluation that increases statistical power and decreases uncertainty, and it is not appropriate to assign LSEs from pooled analyses of individual epidemiological studies.

Presentation of epidemiological data for radon and radon progeny in this updated Toxicological Profile for Radon is focused on results of pooled data from individual studies of occupationally-exposed cohorts

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and pooled data from individual studies that assessed residential exposure. Refer to the introductory statement of Section 3.2.1 for additional information regarding presentation of epidemiological data for radon and radon progeny.

A User's Guide has been provided at the end of this profile (see Appendix B).

3.2.1 Inhalation Exposure

Epidemiological studies designed to assess human health risks from exposure to radon mainly consist of: (1) cohort mortality studies of underground miners that investigated possible associations between lung cancer and individual exposure to radon or radon progeny, (2) residential case-control studies that investigated possible associations between lung cancer cases and residential radon levels using estimates of individual exposure for lung cancer cases as well as controls, and (3) ecological studies that investigated possible associations between rates of selected diseases within a geographic population and some measure of average radon levels within the same defined geographic region. It should be noted that there is no known threshold dose for exposure to alpha radiation from sources including radon and radon progeny, and there is evidence of an inverse exposure rate response at low dose rates (i.e., for a given total exposure, the effect might be greater if delivered at a lower rate over a longer time period). The response relative to increased radon progeny exposure was 25 times larger for nonsmokers (HPA 2009) and tended to decrease with time since the exposure ended, attained age since exposure ended, and exposure duration or exposure rate effect. This apparent inverse dose rate effect may not be real since it was predicated on effects observed for the most highly exposed individuals (early miners in highly dusty environments) for which radon progeny were not measured and equilibrium factors had to be assumed, making dose assignments more uncertain (Lubin et al. 1995b). Also, the portion of the estimated radon cancer risk that is due to silica dust is yet to be evaluated in mining studies before 2000 since crystalline silica was not recognized by the International Agency for Research on Cancer (IARC) as a known human carcinogen until 1997 (IARC 1997). Studies since then have found a high correlation between radon and silica regarding lung cancer and concluded that exposure to quartz can be an important confounder (Bergdahl et al. 2010).

Compelling evidence of radon-induced health effects in humans derives from numerous studies of underground miners, particularly uranium miners exposed beginning in the middle part of the twentieth century in the United States and several European countries. Although these cohort mortality studies typically involved rather crude estimates of exposure to high levels of radon in the working environment

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and inherent uncertainty due to confounding factors such as smoking status and coexposure to known or suspected human carcinogens (diesel exhaust and arsenic), the results nevertheless consistently demonstrate increased risk of lung cancer with increasing exposure to radon in the working environment. These results are consistent across the various individual studies of mining cohorts and with analyses of pooled data from multiple cohorts. However, the miner studies were completed prior to crystalline silica and diesel exhaust being designated as known and suspected human carcinogens, respectively. The highest exposure groups in those studies tended to receive most of their dose before adequate ventilation was established to reduce mine air dust. An assessment of a cohort of iron ore miners with exposure information for radon, diesel exhaust, and silica found excess lung cancers (relative risk [RR] 5.65; 95% confidence interval [CI] 3.15–10.14) in a group of workers at the Malmberget mine with radon exposure >80 mBq-year/m³ (Bergdahl et al. 2010). After accounting for silica exposure, the RR was only 3.90 (95% CI 1.21–12.55). The study authors concluded that accounting for silica exposure in epidemiological studies involving exposure to both radon and silica is important to prevent overestimating the cancer risk from radon. This high correlation between radon, inorganic arsenic, and silica was also reported for a cohort of German uranium miners (Taeger et al. 2008, 2009).

Reported associations between radon and lung cancer in the mining cohorts raised concern regarding the potential health effects of radon in homes, where levels are usually lower than those experienced in mining cohorts and do not include confounding by arsenic and silica dust. Numerous residential case-control studies of lung cancer have been performed in the United States and in many other countries, including Canada, China, Finland, Germany, Sweden, and the United Kingdom. Some of these studies reported positive or weakly positive associations between lung cancer risk and residential radon concentrations, and others suggested that radon reduced the cancer risk, whereas no consistent associations were observed in others. None of the residential case-control studies available for the pooling reported a statistically significant negative association (i.e., decreasing cancer risk in association with increasing radon exposure). Limitations of these studies include: (1) uncertainty in estimating long-term radon levels from relatively few prospective and/or retrospective periodic measurements of radon levels in a particular location; (2) uncertainty in assumptions regarding radon levels in homes where measurements were not made, length of residence and history of prior residences; and (3) accuracy of reported data on confounding factors such as smoking history or active smoker in the home, or including different percentages of smokers in the control and exposed groups. The individual residential case-control studies typically employed relatively low numbers of cases and matched controls, which limits the statistical power of an individual study to identify a statistically significant association between radon exposure and an adverse health outcome such as lung cancer. The statistical power is further reduced by

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measurement error, and residential mobility. In order to more precisely estimate risk, most of the residential study investigators have pooled data from their studies. The pooled analyses have found statistically significant, positive associations between lung cancer and residential radon levels among smokers, but not among lifelong nonsmokers (Darby et al. 2005).

Several ecological studies have been performed to assess possible relationships between selected cancers and estimated radon levels within particular geographic regions where environmental radon levels appear to be higher than other geographic regions. Typically, estimates of mean radon levels for the geographic regions were significantly elevated, but were based on relatively few actual measurements of radon levels in homes in the region and were not matched to individuals. This is problematic because radon (particularly indoor) levels can vary greatly between residences in a particular geographic region. Additional sources of uncertainty in methodology used to estimate radon levels in ecological studies include use of current exposure to represent past exposure, inherent error in measuring devices, use of indirect measures of indoor concentrations as an index of indoor radon exposure, use of sample measurements rather than total-population data, and estimation of individual exposure from group data (Greenland et al. 1989; Morgenstern 1995; Stidley and Samet 1993). Other factors that can lead to inaccurate results regarding associations between exposure to radon and lung cancer include inadequate control of confounding, model misspecification, and misclassification of factors such as health end points, job classifications, and exposure. Results of available ecological studies assessing possible associations between environmental radon levels and lung cancer incidence are mixed; reports include positive and negative associations, as well as no significant associations. Several ecological studies have indicated positive associations between radon levels and selected types of leukemia. Statistically significant associations between radon levels and leukemia were also reported in a miner cohort study (Řeřicha et al. 2006), but not in residential case-control studies from which outcomes and exposures were more accurately matched to individuals.

The health effects chapter of this toxicological profile for radon focuses, primarily, on health effects observed in studies of occupationally-exposed miners and results of pooled analyses of residential case-control studies. Results of animal studies provide additional support to the compelling evidence of radon-induced lung cancer in the miner cohorts and to the evidence of radon-induced lung tumors from results of pooled analyses of residential case-control studies, especially among cigarette smokers. Since these studies are discussed in various sections of the profile, the general design features, attributes, limitations and major findings of the studies that form the bases for conclusions regarding the epidemiological evidence of health effects of radon exposures in humans are provided here.

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Mining cohorts have been followed for several decades or more. Continued follow-up and refined assessments of the most widely-studied mining cohorts have resulted in improved exposure estimates and more complete categorization of individuals according to cause of death, mining history, and smoking status. However, until recently, studies of mining cohorts did not address confounding by silica exposure since crystalline silica was not recognized as a known human carcinogen before most of these studies were published. Assessments also did not necessarily include adjustments for confounding exposures to arsenic and/or diesel exhaust. The bulk of health effects information for the mining cohorts reported in this toxicological profile for radon derives from the most recent analyses of pooled data from 11 mining cohorts (Lubin et al. 1997; NAS 1999a; NIH 1994) using the most recent and comprehensive follow-up results from available studies of individual mining cohorts. Requirements for inclusion of a particular cohort in the analysis of pooled results included: (1) a minimum of 40 lung cancer deaths and (2) estimates of radon progeny exposure in units of WLM for each member of the cohort based on historical measurements of either radon or radon progeny. All 11 studies reported positive associations between lung cancer mortality and radon progeny exposure. For all subjects in each study cohort, person-years were accumulated from the date of entry (based on a minimum time of employment or the occurrence of a medical examination in some studies). A latency period of 5 years was incorporated to represent the expected minimum time necessary for a transformed cell to result in death from lung cancer. Although the accuracy of exposure estimates varied widely among the individual study cohorts, no attempt was made to restrict or limit the role of any particular cohort in the combined analysis. Relative risk for lung cancer was calculated as a function of cumulative WLM after adjustments for cohort, age, other occupational exposures (except silica dust), and ethnicity (NIH 1994). Selected characteristics of the individual cohorts and pooled data are presented in Table 3-1, as well as relative risks of lung cancer mortality for selected categories of cumulative WLM. The results provide evidence for increasing risk of lung cancer mortality with increasing cumulative WLM. Updated analysis of the 11 mining cohorts that contributed to the pooled data of NIH (1994) was particularly focused on relative risk of lung cancer in the miners exposed to relatively low cumulative WLM (Lubin et al. 1997); results demonstrate significant risk of lung cancer mortality at well below 100 WLM (Table 3-2). Excess relative risks (ERRs) for lung cancer mortality (excess risk per WLM) were estimated to be 0.0117/WLM (95% CI 0.002–0.025) for exposures <50 WLM and 0.0080/WLM (95% CI 0.003–0.014) for exposures <100 WLM.

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Table 3-1. Selected Characteristics and Exposure Data for Individual Miner Cohort Studies Included in the Analysis of Pooled Data from the Individual Studies, and Lung Cancer Mortality Rates and Relative Risks by Cumulative WLM for Pooled Data^a

| Study cohort | Mine type | Follow-up | | Non-exposed workers | | Exposed workers and mean cumulative WLM | | |
|---------------------|-----------|-----------|----------------|---------------------|--------------|---|--------------|-------|
| | | Period | Length (years) | Number | Person-years | Number | Person-years | WLM |
| China | Tin | 1976–1987 | 10.2 | 3,494 | 39,985 | 13,649 | 135,357 | 277.4 |
| Czech Republic | Uranium | 1952–1990 | 25.2 | 0 | 4,216 | 4,284 | 103,652 | 198.7 |
| Colorado | Uranium | 1950–1987 | 24.6 | 0 | 7,403 | 3,347 | 75,032 | 807.2 |
| Ontario | Uranium | 1955–1986 | 17.8 | 0 | 61,017 | 21,346 | 319,701 | 30.8 |
| Newfoundland | Fluorspar | 1950–1984 | 23.3 | 337 | 13,713 | 1,751 | 35,029 | 367.3 |
| Sweden | Iron | 1951–1991 | 25.7 | 0 | 841 | 1,294 | 32,452 | 80.6 |
| New Mexico | Uranium | 1943–1985 | 17.0 | 12 | 12,152 | 3,457 | 46,797 | 110.3 |
| Beaverlodge | Uranium | 1950–1980 | 14.0 | 1,591 | 50,345 | 6,895 | 68,040 | 17.2 |
| Port Radium | Uranium | 1950–1980 | 25.2 | 683 | 22,222 | 1,420 | 30,454 | 242.8 |
| Radium Hill | Uranium | 1948–1987 | 21.9 | 1,059 | 26,301 | 1,457 | 25,549 | 7.6 |
| France | Uranium | 1948–1986 | 24.7 | 16 | 4,556 | 1,769 | 39,487 | 68.7 |
| Totals ^b | | | | 7,176 | 242,332 | 60,570 | 908,983 | |
| Averages | | | 17.2 | | | | | 161.6 |

| Cumulative WLM | Lung cancer cases | Person-years | Mean WLM | Relative risk ^d (95% CI) |
|----------------|-------------------|--------------|--------------------|-------------------------------------|
| 0 | 107 | 214,089 | 0.0 | 1.00 |
| 1–49 | 367 | 502,585 | 14.8 | 1.03 (0.8–1.4) |
| 50–99 | 212 | 118,196 | 73.0 | 1.30 (1.0–1.7) |
| 100–199 | 462 | 132,207 | 144.8 | 1.74 (1.3–2.3) |
| 200–399 | 511 | 91,429 | 280.4 | 2.24 (1.7–3.0) |
| 400–799 | 612 | 65,105 | 551.7 | 2.97 (2.2–3.9) |
| 800–1,599 | 294 | 27,204 | 1105.1 | 4.06 (3.0–5.4) |
| ≥1,600 | 140 | 10,336 | 2408.4 | 10.2 (7.4–14.0) |
| Totals | 2,705 | 1,161,150 | 130.6 ^c | |

^aTable entries include 5-year lag interval for radon progeny exposure.

^bTotals adjusted for 115 workers (including 12 lung cancer cases) who were included in both New Mexico and Colorado cohorts.

^cMean WLM among exposed miners is 160.2.

^dAdjusted for cohort, age, other occupational exposures, and ethnicity.

CI = confidence interval; WLM = working level months

Source: NIH 1994

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Table 3-2. Selected Results from Analysis of Pooled Data from 11 Mining Cohorts^a, Based on Deciles of Case Exposures That Were Each Under 100 WLM^b

| Cumulative WLM | Lung cancer cases ^c | Person-years | Mean WLM | Relative risk ^d (95% CI) |
|----------------|--------------------------------|--------------|----------|-------------------------------------|
| 0 | 115 | 274,161 | 0.0 | 1.00 |
| 0.1–3.5 | 56 | 111,424 | 2.4 | 1.37 (1.0–2.0) |
| 3.6–6.9 | 56 | 95,727 | 5.3 | 1.14 (0.8–1.7) |
| 7.0–15.1 | 56 | 72,914 | 12.4 | 1.16 (0.8–1.7) |
| 15.2–21.2 | 57 | 67,149 | 17.3 | 1.45 (1.0–2.2) |
| 21.3–35.4 | 56 | 57,890 | 33.1 | 1.50 (1.0–2.2) |
| 35.5–43.5 | 57 | 42,068 | 38.6 | 1.53 (1.0–2.2) |
| 43.6–59.4 | 56 | 25,622 | 53.2 | 1.69 (1.1–2.5) |
| 59.5–70.3 | 56 | 40,220 | 63.3 | 1.78 (1.2–2.6) |
| 70.4–86.5 | 56 | 28,076 | 81.1 | 1.68 (1.1–2.5) |
| 86.6–99.9 | 56 | 23,682 | 91.4 | 1.86 (1.2–2.8) |

^aThe 11 mining cohorts and reports used for the pooled analysis included China (Xuan et al. 1993), Sweden (Radford and Renard 1984), Newfoundland (Morrison et al. 1988), Czech Republic (Ševc et al. 1988; Tomášek et al. 1994b), Colorado (Hornung and Meinhardt 1987; Hornung et al. 1995), Ontario (Kusiak et al. 1993), New Mexico (Samet et al. 1991), Beaverlodge (Howe et al. 1986), Port Radium (Howe et al. 1987), Radium Hill (Woodward et al. 1991), and France (Tirmarche et al. 1993).

^bTable entries include 5-year lag interval for radon progeny exposure.

^cTotals adjusted for 115 workers (including 12 lung cancer cases) who were included in both New Mexico and Colorado cohorts.

^dAdjusted for cohort, age, other occupational exposures, and ethnicity; excess relative risks for lung cancer mortality were 0.0117 per WLM (95% CI: 0.002–0.025) for exposures <50 WLM and 0.0080 per WLM (95% CI: 0.003–0.014) for exposures <100 WLM.

CI = confidence interval; WLM = working level months

Source: Lubin et al. 1997

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Assessments of pooled data from major residential case-control studies include a combined analysis of 2 China case-control studies (Lubin et al. 2004), a combined analysis of 7 North American case-control studies (Krewski et al. 2005, 2006), and a combined analysis of 13 European case-control studies (Darby et al. 2005, 2006).

The combined analysis of the residential case-control studies in China included a study that assessed all incident lung cancer cases recorded with the Shenyang Cancer Registry and diagnosed between September 1985 and September 1987 (Blot et al. 1990; Xu et al. 1989) and all incident lung cancer cases occurring in two rural prefectures of Gansu Province between June 1994 and April 1998 (Wang et al. 2002). The combined analysis included 1,050 lung cancer cases and 1,996 controls (Lubin et al. 2004). As shown in Table 3-3, odds ratios (ORs) increased significantly with increasing radon concentration. For subjects residing in the current home for ≥ 30 years, the OR at 100 Bq/m³ was 1.32 (95% CI 1.07–1.91).

The individual case-control studies that contributed to the combined analysis of North American case-control studies (Krewski et al. 2005, 2006) were performed in regions of New Jersey, the Canadian Province of Winnipeg, Missouri, Iowa, Connecticut, and Utah-South Idaho. Requirements for inclusion in the combined analysis of North American case-control studies included: (1) ascertainment of at least 200 lung cancer cases (histologically or cytologically confirmed); (2) radon exposure estimates based primarily on long-term α -track detectors located in living areas of homes; and (3) in-person or telephone interviews with subjects or next of kin to obtain data on a variety of demographic, socioeconomic, and smoking-related factors. Of 10,127 total subjects in the 7 North American case-control studies, 765 subjects were excluded from the pooled analysis due to no radon measurements, no residence data within a 5–30-year time exposure window prior to the index date, or insufficient smoking data. The 5–30-year time exposure window presumes that neither radon exposure within 5 years of lung cancer occurrence nor 30 years prior to the index date contributes to lung cancer, although the window is presumed to be generally reflective of a biologically relevant exposure. Thus, the combined analysis included 4,081 lung cancer cases and 5,281 matched controls (Krewski et al. 2006). Selected characteristics of the study subjects and exposure estimates are presented in Table 3-4, along with ORs for lung cancer from pooled data without restriction and ORs resulting from restriction to subjects residing in one or two houses with ≥ 20 years of the residence time covered by α -track monitors. All analyses of the data were conducted using conditional likelihood regression for matched or stratified data and included covariates for sex, age at index date, number of cigarettes smoked per day, duration of smoking, and an indicator variable for each study. An excess odds ratio (EOR) was 0.10 per 100 Bq/m³

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Table 3-3. ORs for Lung Cancer from Combined Analysis of Two China Residential Case-Control Studies (Using a 5–30-Year Exposure Time Window)

| ORs for lung cancer | | | | |
|---|-----------|--------------------|----------|-----------------------------|
| Radon concentration | | Number of subjects | | OR ^a (95% CI) |
| Bq/m ³ | pCi/L | Cases | Controls | |
| <100 | <2.70 | 164 | 298 | 1.00 |
| 100–149 | 2.70–4.01 | 223 | 387 | 1.13 (0.94–1.31) |
| 150–199 | 4.05–5.38 | 198 | 354 | 1.05 (0.86–1.27) |
| 200–249 | 5.41–6.73 | 181 | 372 | 1.14 (0.90–1.45) |
| 250–299 | 6.76–8.08 | 114 | 256 | 1.22 (0.95–1.56) |
| ≥300 | ≥8.11 | 148 | 307 | 1.29 (0.93–1.80) |
| Excess OR (β)=0.133 per 100 Bq/m ³ (95% CI 0.01–0.36) ^b | | | | |
| Excess ORs by years covered by radon detectors and residential mobility within the 5–30-year exposure time window prior to enrollment | | | | |
| Years in exposure time window | | 25 | 20–24 | <20 |
| Excess OR | | 0.319 | -0.134 | -0.072 |
| Number of homes | | 1 | 2 | ≥3 |
| Excess OR | | 0.332 | -0.071 | 0.099 |

^aORs adjusted for sex, age, smoking risk, years in exposure time window, and number of homes inhabited in the exposure time window.

^bBased on linear model: $OR(x)=1+\beta x$, where x is the radon concentration in the exposure time window.

CI = confidence interval; OR = odds ratio

Source: Lubin et al. 2004

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(95% CI -0.1–0.28) for the unrestricted dataset, indicating that radon was not associated with residential lung cancer, but the EOR increased to 0.18 per 100 Bq/m³ (95% CI 0.02–0.43) when restricting to subjects residing in one or two houses with ≥ 20 years of the residence time covered by α -track monitors. This combined analysis provides evidence of an association between residential radon and lung cancer risk (Table 3-4). Histologically, no effect of radon concentration was found for any specific lung cancer type.

The analysis of pooled data from residential case-control studies in 13 European studies (Darby et al. 2005, 2006) included Austria, the Czech Republic, nationwide Finland, south Finland, France, eastern Germany, western Germany, Italy, Spain, nationwide Sweden, never smokers in Sweden, Stockholm Sweden, and the United Kingdom. The pooled data included 7,148 lung cancer cases and 14,208 controls. Inclusion in the analysis required detailed residential histories for at least 15 years, at least 2 months of measurements of radon gas concentrations that were likely to be representative of levels experienced by the study subjects during their tenure in the residences, and details regarding smoking habits. Each study in the pooled analysis included at least 150 lung cancer cases and 150 control subjects. Results of this analysis provide additional evidence of an association between residential radon and lung cancer risk, but mostly among smokers and recent ex-smokers for which the risk was as much as 25 times higher than for never smokers. The evidence for smokers includes statistically significant relative risks at exposure concentrations ≥ 400 Bq/m³ (10.8 pCi/L), an ERR of 0.084 per 100 Bq/m³ (95% CI 0.03–0.158) for the full range of observed radon concentrations, and ERRs of 0.140 per 100 Bq/m³ (95% CI 0.004–0.309) for exposure concentrations < 200 Bq/m³ (< 5.4 pCi/L), 0.095 per 100 Bq/m³ (95% CI 0.005–0.206) for exposure concentrations < 400 Bq/m³ (< 10.8 pCi/L), and 0.078 per 100 Bq/m³ (95% CI 0.012–0.164) for exposure concentrations < 800 Bq/m³ (< 21.6 pCi/L) (Table 3-5). For lifelong nonsmokers, an ERR of 0.106 per 100 Bq/m³ (95% CI 0.003–0.280) was observed for the full range of observed radon concentrations.

Although the dose-response coefficients from the mining studies and residential studies are expressed in different units of exposure (i.e., WLM vs. Bq-year/m³), they can be compared by applying the relationship described above, namely that 1 pCi/L (37 Bq/m³) of continuous exposure throughout the year (i.e., 37 Bq-year/m³) is equivalent to 0.144 WLM for that year. Thus, a 25-year exposure at 200 Bq/m³ (5.4 pCi/L) would be equivalent to a cumulative exposure of 19.5 WLM. Using this conversion factor, an estimated excess relative risk of 0.0117/WLM at occupational exposures < 50 WLM (Lubin et al. 1997) would be roughly equivalent to an ERR of 0.114 per 100 Bq/m³, assuming that the miners were not exposed to silica dust since accounting has not yet been conducted for confounding by this carcinogen.

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Table 3-4. Selected Characteristics of Study Subjects, Exposure Estimates, and ORs for Lung Cancer from Combined Analysis of Seven North American Residential Case-Control Studies (Using a 5–30-Year Exposure Time Window)

| Region | Number of subjects ^a | | Time-weighted average radon concentration in Bq/m ³ | | |
|-------------|---------------------------------|----------|--|----------|--------------|
| | Lung cancer cases | Controls | Lung cancer cases | Controls | All subjects |
| New Jersey | 480 | 442 | 26.5 | 24.9 | 25.7 |
| Winnipeg | 708 | 722 | 137.4 | 146.9 | 142.2 |
| Missouri-I | 530 | 1,177 | 62.2 | 62.9 | 62.7 |
| Missouri-II | 477 | 516 | 55.3 | 56.1 | 55.7 |
| Iowa | 412 | 613 | 136.2 | 121.3 | 127.3 |
| Connecticut | 963 | 949 | 32.2 | 32.8 | 32.5 |
| Utah-Idaho | 511 | 862 | 55.4 | 58.1 | 57.1 |

| ORs for lung cancer | | | | |
|---------------------|-----------|--------------------|----------|-----------------------------|
| Radon concentration | | Number of subjects | | OR ^b (95% CI) |
| Bq/m ³ | pCi/L | Cases | Controls | |
| <25 | <0.68 | 994 | 1,055 | 1.00 |
| 25–49 | 0.68–1.32 | 1,169 | 1,549 | 1.13 (0.94–1.31) |
| 50–74 | 1.35–2.00 | 704 | 1,087 | 1.05 (0.86–1.27) |
| 75–99 | 2.03–2.68 | 356 | 507 | 1.14 (0.90–1.45) |
| 100–149 | 2.70–4.03 | 513 | 602 | 1.22 (0.95–1.56) |
| 150–199 | 4.05–5.38 | 166 | 229 | 1.19 (0.86–1.66) |
| ≥200 | ≥5.45 | 179 | 252 | 1.29 (0.93–1.80) |

Excess OR (β)=0.10 per 100 Bq/m³ (95% CI -0.01–0.28)^c

| ORs for lung cancer with data restricted to subjects residing in one or two houses in the exposure window with ≥20 years covered by α -track air monitors | | | | |
|--|-----------|--------------------|----------|-----------------------------|
| Radon concentration | | Number of subjects | | OR ^b (95% CI) |
| Bq/m ³ | pCi/L | Cases | Controls | |
| <25 | <0.68 | 503 | 596 | 1.00 |
| 25–49 | 0.68–1.32 | 481 | 717 | 1.01 (0.80–1.28) |
| 50–74 | 1.35–2.00 | 295 | 418 | 1.29 (0.98–1.70) |
| 75–99 | 2.03–2.68 | 181 | 293 | 1.22 (0.88–1.69) |
| 100–149 | 2.70–4.03 | 202 | 282 | 1.28 (0.91–1.78) |
| 150–199 | 4.05–5.38 | 115 | 160 | 1.41 (0.83–2.14) |
| ≥200 | ≥5.45 | 133 | 185 | 1.29 (0.91–2.06) |

Excess OR (β)=0.18 per 100 Bq/m³ (95% CI 0.02–0.43)^c

^aFor the combined analysis of the 7 North American residential case-control studies, 339 lung cancer cases and 426 control subjects were excluded based on lack of smoking, radon, and/or residence data.

^bORs stratified by sex and categories of age, duration of smoking, number of cigarettes smoked per day, number of residences, and years with α -track measurements in the exposure time window.

^cBased on linear model: $OR(x)=1+\beta x$, where x is the radon concentration in the exposure time window.

CI = confidence interval; OR = odds ratio

Source: Krewski et al. 2006

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Table 3-5. Relative Risk and Excess Relative Risk of Lung Cancer by Radon Level in Homes 5–34 Years Previously, Estimated from the Pooled Data for 13 European Residential Case-Control Studies

| Radon concentration | | | Number of subjects | | |
|----------------------------|---------------------------|--------------|--------------------|----------|------------------|
| Range (Bq/m ³) | Mean (Bq/m ³) | Mean (pCi/L) | Lung cancer cases | Controls | RR (95% CI) |
| <25 | 17 | 0.46 | 566 | 1,474 | 1.00 (0.87–1.15) |
| 25–49 | 39 | 1.05 | 1,999 | 3,905 | 1.06 (0.98–1.15) |
| 50–99 | 71 | 1.92 | 2,618 | 5,033 | 1.03 (0.96–1.10) |
| 100–199 | 136 | 3.68 | 1,296 | 2,247 | 1.20 (1.08–1.32) |
| 200–399 | 273 | 7.38 | 434 | 936 | 1.18 (0.99–1.42) |
| 400–799 | 542 | 14.65 | 169 | 498 | 1.43 (1.06–1.92) |
| ≥800 | 1,204 | 32.54 | 66 | 115 | 2.02 (1.24–3.31) |

Excess relative risk for lung cancer according to selected ranges of radon concentrations

| Range of radon concentrations | | Lung cancer cases | Controls | ERR per 100 Bq/m ³ (95% CI) |
|-------------------------------|------------|-------------------|----------|--|
| <800 Bq/m ³ | 21.6 pCi/L | 7,082 | 14,093 | 0.078 (0.012–0.164) |
| <400 Bq/m ³ | 10.8 pCi/L | 6,913 | 13,595 | 0.095 (0.005–0.206) |
| <200 Bq/m ³ | 5.4 pCi/L | 6,479 | 12,659 | 0.140 (0.004–0.309) |
| <100 Bq/m ³ | 2.7 pCi/L | 5,183 | 10,412 | 0.025 (-0.192–0.306) |
| All radon concentrations | | 7,148 | 14,208 | 0.084 (0.030–0.158) |

CI = confidence interval; ERR = excess relative risk; RR = relative risk

Source: Darby et al. 2006

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This value is similar to the estimates for excess relative risk ($0.084/\text{Bq}/\text{m}^3$) estimated from the analysis of pooled data from the 13 European case-control studies (Darby et al. 2005, 2006) and EOR (0.18 per $100 \text{ Bq}/\text{m}^3$) estimated from the pooled analysis of the North American residential case-control studies restricted to subjects residing in one or two houses with ≥ 20 years of the residence time covered by α -track monitors (Krewski et al. 2006). Based on this comparison, the studies of mining cohorts and the residential studies appear to converge on similar estimates for the relationship between exposure to radon (and its progeny) and risk of lung cancer mortality. However, since the miners were exposed to silica dust and those studies did not assess confounding by this substance (which was confirmed as a known human carcinogen after those studies were published), attempts to correlate radon risk from residential and mining studies may be premature. This is emphasized in the re-assessed results of Swedish mines in which strong correlation was found between radon and silica, and accounting for silica reduced the RR previously attributed to radon by approximately 30%, from 5.65 to 3.90 (Bergdahl et al. 2010).

Available animal data consist mainly of inhalation studies performed at the University of Rochester (UR) in the 1950s and 1960s using rats, mice, and dogs (AEC 1961, 1964, 1966; Morken 1955, 1973); at the Pacific Northwest Laboratory (PNL, presently Pacific Northwest National Laboratory [PNNL]) between the 1960s and 1980s using rats, dogs, and hamsters (Cross 1988, 1994; Cross et al. 1981a, 1981b, 1984; Dagle et al. 1992; Gilbert et al. 1996; NIEHS 1978; Palmer et al. 1973); and at laboratories in France using rats (Chameaud et al. 1974, 1980, 1982a, 1982b, 1984; Monchaux 2004; Monchaux and Morlier 2002; Monchaux et al. 1999; Morlier et al. 1992, 1994). Most of these studies employed exposure levels that were many orders of magnitude higher than those considered to be relevant to human health. Discussion of animal studies in Section 3.2.1 is limited to studies that employed exposure levels considered relevant to plausible human exposure scenarios (Chameaud et al. 1984; Morlier et al. 1994).

3.2.1.1 Death

Possible associations between exposure to radon and lung cancer mortality among underground miners are discussed in Section 3.2.1.7 (Cancer).

Excess mortality from noncancer diseases reported in some of the mining cohorts include all noncancer respiratory diseases, pneumoconioses, emphysema, interstitial pneumonitis, other (unspecified) chronic obstructive respiratory diseases, and tuberculosis (Lundin et al. 1971; Muller et al. 1985; Roscoe 1997; Roscoe et al. 1989, 1995; Samet et al. 1991; Tirmarche et al. 1993; Waxweiler et al. 1981). However, confounding factors such as exposure to other respiratory toxicants (most notably arsenic and silica dust),

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ethnicity, smoking history, and work experience were likely major contributors to mortalities from noncancer respiratory diseases. A statistically significant excess of mortality due to chronic nephritis and renal sclerosis was also reported in the U.S. uranium miner cohort, although it is unclear whether this was related to exposure to radon, uranium ore, or other mining conditions or to nonmining factors (Waxweiler et al. 1981).

No significant association was observed between cumulative exposure to radon progeny and death from cardiovascular diseases in cohorts of German uranium miners (Kreuzer et al. 2010) or Newfoundland fluorspar miners (Villeneuve et al. 2007a).

Limited information is available regarding exposure to radon and death in animals. No significant effects on longevity were observed in male Sprague-Dawley rats exposed to atmospheres of radon and radon progeny for 6 hours/day, 5 days/week during 18 months to obtain a cumulative exposure of 25 WLM (Morlier et al. 1994) or in rats exposed to a cumulative exposure of 20 WLM (1 hour exposures twice weekly for 42 total exposures) or 40 WLM (1-hour exposures twice weekly for 82 total exposures) (Chameaud et al. 1984). It should be noted that these studies employed relatively low dose rates.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, hepatic, dermal, or body weight effects after inhalation exposure to radon and its progeny at exposure levels considered relevant to human health.

Respiratory Effects. Possible associations between exposure to radon and lung cancer are discussed in Section 3.2.1.7. Adverse noncancer respiratory effects have been observed in humans under occupational conditions and in laboratory animals exposed to radon and its progeny. Some studies of miner cohorts identified excess cases of nonmalignant respiratory diseases such as asthma, bronchitis, pneumoconioses, emphysema, interstitial pneumonitis, pulmonary fibrosis, and tuberculosis (Boice et al. 2008; Fox et al. 1981; Lundin et al. 1971; Muller et al. 1985; Roscoe 1997; Roscoe et al. 1989, 1995; Samet et al. 1991; Tirmarche et al. 1993; Waxweiler et al. 1981). However, potential confounding by smoking and respirable dust, especially crystalline silica dust, were likely major contributors to mortalities from noncancer respiratory diseases. Excess mortality associated with exposure to silica dust was reported in California diatomaceous earth miners for which the standard mortality ratio (SMR) was 2.01 (95% CI 1.56–2.55). The mortality rate increased sharply with exposure using a 15-year latency, which is longer

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than the 5-year latency used for most miner and residential radon studies (Checkoway et al. 1997). Chronic lung disease was reported to increase with increasing cumulative exposure to radiation and with cigarette smoking (Archer 1980). In addition, nonsmoking uranium miners were also reported to have increased deaths from nonmalignant respiratory disease compared to a nonsmoking U.S. veteran cohort (Roscoe et al. 1989). For non-miners, the rate of chronic obstructive pulmonary disease (COPD) was reported to increase with increasing radon exposure (Turner et al. 2012).

Alterations in respiratory function have been reported in studies of U.S. uranium miners (Archer et al. 1964; Samet et al. 1984a; Trapp et al. 1970). Archer et al. (1964) reported decrements in pulmonary function with increasing cumulative exposure; however, the study also noted that pulmonary disability was affected by age and smoking more than by radiation exposure. Samet et al. (1984a) reported significantly increased prevalence of dyspnea with increasing duration of underground mining. Evaluations of these respiratory end points did not include assessment of the effects of each of the other possible mine pollutants, such as ore dust, silica, or diesel engine exhaust.

No information was located regarding respiratory effects in animals following exposure to radon and its progeny at concentrations considered relevant to human health.

Cardiovascular Effects. No significant association was observed between cumulative exposure to radon progeny and death from cardiovascular diseases in cohorts of German uranium miners (Kreuzer et al. 2010) or Newfoundland fluorspar miners (Villeneuve et al. 2007a). A significant relationship was noted between cumulative radon exposure and prevalence of mortality from cerebrovascular disease (excess relative risk of 0.49 [95% CI 0.07–1.23] per 100 WLM) in a French cohort study of uranium miners between 1946 and 1999 (Nusinovici et al. 2010). However, the study authors cautioned that a lack of data limited the ability to assess possible confounding by cardiovascular risk factors.

No information was located regarding cardiovascular effects in animals following exposure to radon and its progeny at concentrations considered relevant to human health.

Hematological Effects. No studies were located regarding hematological effects after inhalation exposure to radon at concentrations considered relevant to human health.

Renal Effects. Although a statistically significant increase in mortality due to kidney disease, characterized by chronic nephritis and renal sclerosis, was reported among U.S. uranium miners

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(Waxweiler et al. 1981) and in Canadian miners at the Eldorado mines (Muller et al. 1985), this finding is not generally considered to be related to radon exposure *per se*.

No information was located regarding renal effects in animals following exposure to radon and its progeny.

Ocular Effects. Abdelkawi et al. (2008) reported significantly increased refractory index, decreased protein concentration, and increased protein molecular weight after 6 weeks of exposure in the lens and cornea of mice exposed to radon at a mean concentration of 55.8 kBq/m³ (attached fraction of 0.62) for 6 hours/day, 5 days/week for up to 8 weeks. Effective radon lung doses ranged from 20.92 to 83.68 mSv. The study investigators considered the effects on the lens and cornea to have resulted from systemic distribution of inhaled radioactivity. Although the dermal route of exposure was not considered, the permeability of corneal epithelium to atmospheric gases could allow radon at the high concentrations used in the study to diffuse toward and expose both the cornea and lens to alpha radiation.

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects after inhalation exposure to radon at concentrations considered relevant to human health.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects after inhalation exposure to radon at concentrations considered relevant to human health.

3.2.1.5 Reproductive Effects

No maternal or fetal reproductive effects in humans have been attributed to exposure to radon and its progeny. However, a decrease in the secondary sex ratio (males:females) of the children of male underground miners may be related to exposure to radon and its progeny (Dean 1981; Muller et al. 1967; Wiese and Skipper 1986). Ismail and Jaafar (2010) assessed possible relationships between radiation dose to the lungs from radon and radon progeny and rates of infertility within various locations in Iraqi Kurdistan. Radon levels were measured in homes; annual effective lung doses by inhalation of radon and radon progeny were estimated to range from approximately 2 to 6 mSv/yr. The dose to the gonads was not estimated, but would have been lower than that for the lungs and orders of magnitude lower than the

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protracted external radiation doses stated to induce temporary sterility (400 mSv/yr) or permanent sterility (2000 mSv/year). The study authors reported an exponential relationship between annual effective lung dose and the rate of male infertility that is not supported by the reported low estimates of radiation dose. The authors also stated that there were increases in blood and prostate cancers (which influence male fertility), but did not provide quantitative data. Overall, the scientific value of this study is questionable.

No information was located regarding reproductive effects in animals following exposure to radon and its progeny at concentrations considered relevant to human health.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to radon and its progeny.

No information was located regarding developmental effects in animals following exposure to radon and its progeny at concentrations considered relevant to human health.

3.2.1.7 Cancer

Associations between exposure to radon and lung cancer mortality have been examined in studies of underground miners at facilities in the United States (Archer et al. 1973, 1976, 1979; Boice et al. 2008; Checkoway et al. 1985; Gottlieb and Husen 1982; Hornung and Meinhardt 1987; Hornung et al. 1998; Lane et al. 2010; Lubin et al. 1995a, 1995b; Luebeck et al. 1999; Lundin et al. 1971; Moolgavkar et al. 1993; NIH 1994; Roscoe 1997; Roscoe et al. 1989, 1995; Samet et al. 1984b, 1989, 1991, 1994; Schubauer-Berigan et al. 2009; Stayner et al. 1985; Stram et al. 1999; Thomas et al. 1994; Wagoner et al. 1963, 1964; Waxweiler et al. 1981), Australia (Woodward et al. 1991); Brazil (Veiga et al. 2006), Canada (Howe and Stager 1996; Howe et al. 1986, 1987; Kusiak et al. 1993; L'Abbé et al. 1991; Morrison et al. 1985, 1998; Muller et al. 1985), China (Qiao et al. 1989, 1997; Yao et al. 1994), the Czech Republic (Kulich et al. 2011; Ševc et al. 1988, 1993; Tomášek 2002, 2011; Tomášek and Darby 1995; Tomášek and Plaček 1999; Tomášek and Žárská 2004; Tomášek et al. 1993, 1994a, 1994b, 2008), England (Fox et al. 1981; Hodgson and Jones 1990b), France (Amabile et al. 2009; Laurier et al. 2004; Leuraud et al. 2007; Rogel et al. 2002; Tirmarche et al. 1993; Vacquier et al. 2007, 2009), Germany (Brüske-Hohlfeld et al. 2006; Kreuzer et al. 2000, 2010; Schnelzer et al. 2010; Taeger et al. 2006, 2008, 2009; Walsh et al. 2010), Italy (Carta et al. 1994), Norway (Solli et al. 1985), and Sweden (Axelson and Sundell 1978; Bergdahl et al. 2010; Damber and Larsson 1982; Edling and Axelson 1983; Jonsson et al. 2010;

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Jorgensen 1984; Radford and Renard 1984; Snihs 1974). The mining cohorts were primarily uranium miners, but included some cohorts mining other metals, hard rock, or coal.

Lubin et al. (1997) provide combined results from eleven of these cohorts; the results demonstrate increased risk of mortality from lung cancer with increasing WLM (see Table 3-2). The combined data included 115 lung cancer deaths among workers without known occupational exposure to radon and 2,674 lung cancer deaths among exposed miners. Some of these miners had been exposed to more than 10,000 WLM; the mean exposure among the pooled miner data was 162 WLM. In order to make more meaningful comparisons between radon exposure among mining cohorts and residential radon exposure, Lubin et al. (1997) assessed mortality from lung cancer among two groups of workers with the lowest exposure levels (<50 and <100 WLM, respectively). Even in these groups of miners with relatively low-level exposure, relative risk of lung cancer mortality exhibited an apparent linear and statistically significant increasing trend with WLM (in decile categories). RRs for the two highest exposure categories (142.3–250.8 and >250.8 Bq/m³; equivalent to 3.84–6.77 and >6.77 pCi/L, respectively) were 1.28 (95% CI 1.0–1.6) and 1.20 (95% CI 1.0–1.5), respectively. ERRs per WLM were estimated to be 0.0117/WLM (95% CI 0.002–0.025) for exposures <50 WLM and 0.0080/WLM (95% CI 0.003–0.014) for exposures <100 WLM. General patterns of declining excess relative risk per WLM with attained age, time since exposure, and exposure rate were observed in both the unrestricted pooled data and in those restricted to <50 and <100 WLM. Lubin et al. (1997) noted an apparent inadequacy in the fit of the ERR model, but this was not improved using nonlinear or linear threshold models. Lubin et al. (1997) also noted that results for the mining cohorts with relative low-level exposure might not be applicable to residential radon exposure due to uncertainties in estimating miner exposure to radon, radon progeny, and other carcinogens (e.g., silica dust) during the earliest years of mining when ventilation was poor.

Leuraud et al. (2011) assessed the effects of exposure to radon and radon decay products and smoking status on the risk of lung cancer in a combined analysis of 1,046 lung cancer cases and 2,492 controls with detailed radon exposure data and smoking status selected from three major minor cohorts in the Czech Republic (Tomášek et al. 2003), France (Laurier et al. 2004), and Germany (Kreuzer et al. 2010). The combined analysis resulted in an ERR/WLM of 0.010 (95% CI 0.006–0.018) unadjusted for smoking and an ERR/WLM of 0.008 (95% CI 0.004–0.014) after adjustment for smoking, which was based on four categories: never smoker, ex-smoker for ≥10 years, ex-smoker for <10 years, and current smoker. The results of Leuraud et al. (2011) suggest a sub-multiplicative interaction between radon exposure and smoking.

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The results of the miner studies consistently demonstrate significant positive associations between lung cancer and exposure to radon. However, most miner studies were performed prior to the identification of other substances as known human carcinogens (silica dust and arsenic; NTP 2011) or probable human carcinogens (diesel exhaust particulates; Attfield et al. 2012; NTP 2011) in the mining air. Accounting for these carcinogens would likely reduce the calculated impact of radon on lung cancer mortality in the mining cohorts. For example, Xuan et al. (1993) estimated a 75% reduction in the lung cancer risk to a cohort of Chinese tin miners after adjusting for arsenic exposure. Bergdahl et al. (2010) reported decreased lung cancer risk from radon after adjusting for silica exposure within the highest exposure group from a cohort of Swedish iron ore miners. Statistically significant excess lung cancer mortality has been associated with average cumulative exposures to radon progeny as low as 36–39 WLM in Czech and French cohorts of uranium miners (Ševc et al. 1988; Vacquier et al. 2007); exposure levels were higher among many of the other uranium miner cohorts. Vacquier et al. (2009) reported an ERR per 100 WLM of 0.58 ($p < 0.01$) for lung cancer within a cohort of 5,086 French uranium miners (4,133 with positive radon exposure; mean cumulative exposure of 36.6 WLM) and 159 lung cancer cases during 30 years of follow up and noted that higher risk persisted when the effects of hard labor and period of exposure were taken into account. An inverse exposure rate effect (i.e., lower exposure rates for long periods are more hazardous than equivalent cumulative exposure received at higher exposure rates over a shorter time) was evident at relatively high exposure levels (WL) (Hornung et al. 1998; Lubin et al. 1995a, 1997; Luebeck et al. 1999; Moolgavkar et al. 1993; NIH 1994); however, this effect appeared to be attenuated or absent at relatively low exposure levels (Lubin et al. 1995a; NIH 1994; Tomášek et al. 2008). The apparent inverse exposure rate effect could have been associated with using no-threshold models, a restriction that was not required in the European residential assessment (HPA 2009).

Among smoking and nonsmoking uranium miners, the most frequently reported type of lung cancer was small cell lung carcinoma (SCLC) in the early phase of follow-up (Archer et al. 1974; Auerbach et al. 1978; Butler et al. 1986; Gottlieb and Husen 1982; Saccomanno et al. 1971, 1988; Samet 1989). Archer et al. (1974) also noted relatively high rates of epidermoid and adenocarcinomas, while large-cell undifferentiated and other morphological types of lung cancer were seen less frequently. A report on the German uranium mining cohort identified squamous cell carcinoma as the predominant lung tumor cell type, followed by adenocarcinoma and SCLC (Kreuzer et al. 2000). Jonsson et al. (2010) reported lung cancer risk in a cohort of 5,449 male iron ore miners in Sweden; the follow-up period spanned the years 1958–2000. A total of 3,597 of the miners had been exposed to radon; the average cumulative radon exposure was 65 WLM over an average of 14.6 years of employment. For all lung cancers, the ERR per $\text{kBq}\cdot\text{year}/\text{m}^3$ was 0.046 (95% CI 0.015–0.077), which equals an ERR/WLM of 0.022WLM (95% CI

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0.007–0.038). For small cell cancer (55 cases), squamous cell cancer (51 cases), and adenocarcinoma (12 cases), ERRs per kBq-year/m³ were 0.072 (95% CI -0.003–0.147), 0.049 (95% CI -0.003–0.102), and 0.000 (95% CI 0.017–0.017), respectively. After adjusting for cumulative quartz (silica) together with attained age and calendar period, the ERR for all lung cancers was 0.031 per kBq-year/m³ (95% CI 0.009–0.070), which equals an ERR of 0.015 per WLM (95% CI 0.04–0.034).

In a subcohort of 516 white nonsmoking uranium miners (drawn from a larger cohort of U.S. uranium miners), mean exposure was reported as 720 WLM. For this cohort, the mortality risk for lung cancer was found to be 12-fold greater than that of nonsmoking, nonmining U.S. veterans; the SMR was 12.7 (95% CI 8.0–20.1) for lung cancer in nonsmoking mining cohort. No lung cancer deaths were found in nonsmoking miners (Colorado Plateau cohort) who had exposure <465 WLM (Roscoe et al. 1989); continued follow-up of this cohort (1960–2005) revealed SMRs of 2.9 (95% CI 1.8–4.4) for never smokers with cumulative exposure to radon progeny in the range of 400–1,000 WLM and 6.3 (95% CI 4.6–8.5) for never smokers with cumulative exposure to radon progeny ≥1,000 WLM (Schubauer-Berigan et al. (2009). These results for nonsmokers follow a dose rate rather than an inverse dose rate response curve.

Some studies of mining cohorts included assessments of mortality from cancers other than lung cancer. Kreuzer et al. (2010) reported a slight, but statistically significant excess of cancers of the extrathoracic airways and trachea (ERR/WLM = 0.062%; 95% CI 0.002–0.121%) within a cohort of 58,987 male uranium miners at the Wismut mine in Germany with follow-up from 1946 to 2003. Řeřicha et al. (2006) reported significant positive associations between cumulative radon exposures and incidences of leukemia (RR=1.75; 95% CI 1.10–2.78) and incidences of chronic lymphocytic leukemia (CLL) (RR=1.98; 95% CI 1.10–3.59) in a cohort of Czech uranium miners at 110 WLM. In apparent contrast, this same group did not find this relationship to hold in a longer-term follow-up of the same population (Kulich et al. 2011). Möhner et al. (2006, 2010) observed no significant associations between leukemia risk (from acute myeloid leukemia [AML], CLL, or all types) and exposure to radon progeny (from <50 to >1,500 WLM) among 377 leukemia cases and 980 individually matched controls from a cohort of 360,000 uranium miners at the Wismut mine in the former East Germany that supported the Soviet nuclear weapons program. However, the leukemia risk became significant (OR 2.64, 95% CI 1.60–2.35) in the highest dose category when doses were lagged 20 years (Möhner et al. 2010), the same period used by Pelucchi et al. (2006) for the silica dust study, but much longer than 5 years used in other studies in this section. This indicates that the 5-year lag period might be too short. Results of a few other studies indicate statistically significant excessive mortalities from laryngeal, liver, kidney, stomach, and/or gall bladder cancers

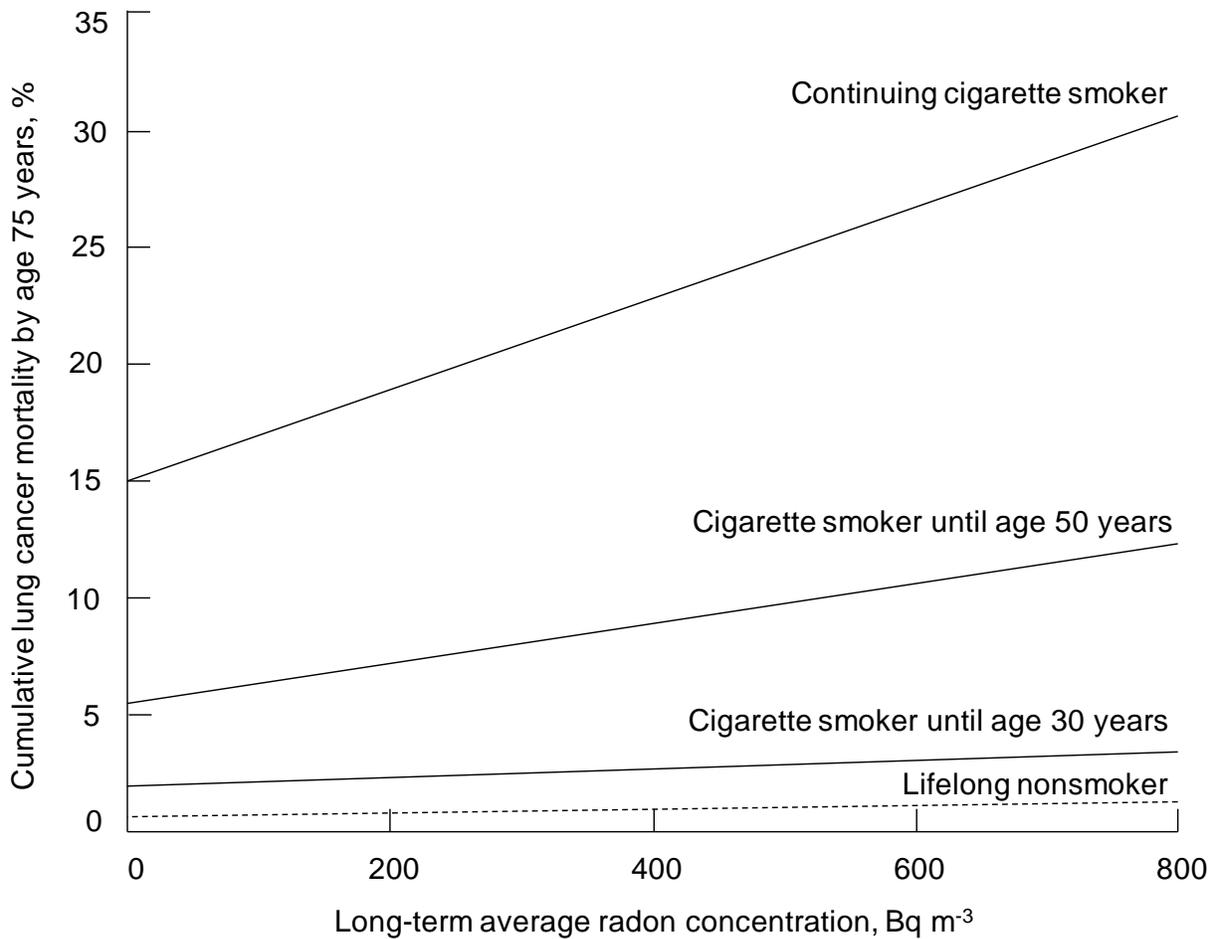
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(Kreuzer et al. 2004, 2008; Tirmarche et al. 1992; Tomášek et al. 1993; Vacquier et al. 2007); however, the excess mortalities from these cancers did not appear to be related to cumulative exposure to radon and were not supported by results from other studies of mining cohorts (Kreuzer et al. 2010; Kulich et al. 2011; Laurier et al. 2004; Möhner et al. 2008).

Numerous residential case-control studies of lung cancer have been performed in the United States and other countries, including Brazil, Canada, China, Croatia, the Czech Republic, Finland, France, Germany, Israel, Italy, Japan, Romania, Spain, Sweden, and the United Kingdom. Some of these studies reported positive or weakly positive associations between lung cancer risk and residential radon concentrations, whereas no significant associations were observed in others. As discussed earlier, recent assessment of available residential case-control studies includes analyses of pooled data from 2 China case-control studies (Lubin et al. 2004), a combined analysis of 7 North American case-control studies (Krewski et al. 2005, 2006), a combined analysis of 13 European case-control studies (Darby et al. 2005, 2006), and a comparative assessment of the three combined analyses (HPA 2009). Pooling resulted in much larger numbers of lung cancer cases and controls than were achieved in individual case-control studies. The results of these analyses of pooled data provide evidence of increased risk for lung cancer with increasing residential levels of radon (Tables 3-3, 3-4, and 3-5) for cigarette smokers, including a statistically significant relative risk of lung cancer at mean radon concentrations $\geq 542 \text{ Bq/m}^3$ (14.65 pCi/L) reported by Darby et al. (2006) (Table 3-5). The HPA (2009) assessment identified flaws that resulted in the China and North American studies overestimating the radon cancer risk. According to the HPA (2009), the European study properly assessed radon risk by using more accurate dosimetry and including more homes, and the resulting radon risk estimate paralleled that of the whole China and North American database. However, the China and North American studies selected only a portion of the database, limiting inclusion to those living in one or two homes with more complete dosimetry, but the manner in which homes were selected would have introduced socioeconomic bias, which in addition to lower dosimetry approach, caused the China and North American studies to overestimate the radon risk. Nevertheless, all three combined analyses support the conclusion that residential radon is carcinogenic. HPA (2009) estimated that the cumulative (absolute) radon-induced lung cancer risk to age 75 for long-term exposure to radon at 0, 100, 200, 400, and 800 Bq/m^3 (0, 2.7, 5.41, 10.81, and 21.62 pCi/L) is 15, 17, 19, 23, and 30%, respectively, for lifetime smokers, and 0.4, 0.5, 0.5, 0.7, and 0.9%, respectively, for lifetime nonsmokers. Overall, the risk for the lifetime nonsmokers was 25 times lower than for the lifetime smokers (Darby et al. 2006; HPA 2009). Figure 3-1 shows the cumulative absolute risk of death from lung cancer by age 75 years relative to long-term average in-home radon concentration for

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Figure 3-1. Cumulative Absolute Risk of Death from Lung Cancer by Age 75 Years Versus Long-Term Average Radon Concentration at Home for Continuing Smokers, Ex-Smokers, and Lifelong Nonsmokers in the United Kingdom



Source: adapted from HPA 2009

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continuing smokers, ex-smokers, and lifelong nonsmokers in the United Kingdom, as reported by Darby et al. (2006) and HPA (2009).

Assessment of the results of residential case-control studies and comparisons between the presently-available pooled results of the China case-control studies (Lubin et al. 2004), North American case-control studies (Krewski et al. 2005, 2006), and European case-control studies (Darby et al. 2005, 2006) must take into account the effects of exposure measurement error and methodological differences in final analyses. Estimates based on measured radon concentrations will likely underestimate the true risks associated with residential radon, due to misclassification of exposure from detector measurement error, spatial radon variations within a home, temporal radon variation, missing data from previously occupied homes that currently are inaccessible, failure to link radon concentrations with subject mobility, and measuring radon gas concentration as a surrogate for radon progeny exposure (Field et al. 1996, 2002). Generally, if exposure misclassification does not differ systematically between cases and controls, the observed results tend to be biased toward the null (for example, the true effect is actually underestimated). In fact, Field et al. (2002) demonstrated that empirical models with improved retrospective radon exposure estimates were more likely to detect an association between prolonged residential radon exposure and lung cancer. Direct comparisons between the pooled results of the China case-control studies (Lubin et al. 2004), North American case-control studies (Krewski et al. 2005, 2006), and those of the European case-control studies (Darby et al. 2005, 2006) are problematic because only the pooled results of the European case-control studies included regression calibration in an attempt to adjust for some of the measurement error.

Turner et al. (2011) recently reported the results of a large prospective study that found positive associations between ecological indicators of residential radon and lung cancer. The study included a cohort of 811,961 individuals from nearly 1.2 million participants recruited in 1982 for the American Cancer Society Cancer Prevention Study-II. The cohort encompasses 2,754 U.S. counties and 3,493 observed lung cancer deaths as of 1988. Ecological estimates of residential radon concentrations were obtained from the Lawrence Berkeley National Laboratory and were intended to represent the average annual radon concentrations in the main living areas of homes by primary county of residence. The study authors reported a significant positive trend between categories of radon concentrations and lung cancer mortality ($p=0.02$), a 15% (95% CI 1–31) increase in risk of lung cancer mortality per 100 Bq/m^3 (2.7 pCi/L) increase in radon, and a 34% (95% CI 7–68) increase in risk of lung cancer mortality among residents with estimated radon concentrations above the EPA guideline value of 148 Bq/m^3 (4 pCi/L).

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Information regarding radon-induced lung cancer in animals exposed to radon and its progeny at concentrations considered relevant to human health includes significantly increased incidences of lung tumors in rats repeatedly exposed to radon and its progeny at cumulative exposures as low as 20–50 WLM (Chameaud et al. 1984; Morlier et al. 1994). These results are consistent with the demonstrated associations between lung cancer risk and exposure to radon and radon progeny in occupationally-exposed miners and residentially-exposed individuals.

3.2.2 Oral Exposure

No studies were located regarding the following health effects, other than cancer, in humans or animals after oral exposure to radon or its progeny:

3.2.2.1 Death

3.2.2.2 Systemic Effects

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

Information regarding cancer in humans after exposure to radon and its progeny in water is limited to ecological studies. As noted earlier, ecological studies are limited by several factors that may include bias in estimated indoor radon levels, inadequate control of confounding, model misspecification, and misclassification. Radon levels were measured in 2,000 public and private wells in 14 counties in Maine (Hess et al. 1983). The county averages were compared to cancer rate by county to determine any degree of correlation. Significant correlation was reported for all lung cancer and all cancers combined, when both sexes were combined, and for lung tumors in females. Confounding factors (e.g., smoking) were not considered in this analysis. In addition, exposure from radon in these water supplies could have been by the inhalation route as well as the oral route. Results of some ecological studies suggest positive associations between radon levels in ground water sources and incidences of cancers, including lung cancer (Hess et al. 1983), all cancers combined (Mose et al. 1990), and childhood cancer (leukemias and all cancers combined) (Collman et al. 1990). In another study, Collman et al. (1988) found no consistent associations between radon concentrations in ground water and cancer mortality. More recent case-cohort

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studies in Finland found no significant associations between mean concentrations of radon in well water and cases of stomach cancer (Auvinen et al. 2005) or bladder or kidney cancer (Kurttio et al. 2006).

No studies were located regarding cancer in animals after oral exposure to radon and its progeny.

3.2.3 Dermal Exposure

3.2.3.1 Death

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, body weight, or metabolic effects in humans or animals following exposure to radon and radon progeny.

Ocular Effects. Abdelkawi et al. (2008) reported increased refractory index, increased molecular weight, and decreased concentration of soluble proteins in the cornea and lens of mice exposed to radon at a mean concentration of 55.8 kBq/m³ for 6 hours/day, 5 days/week for up to 8 weeks. Effective radon lung doses ranged from 20.92 to 83.68 mSv for combined dermal contact and inhaled radioactivity. Corneal effects were observed after 2 weeks, followed by lenticular effects (after 6 weeks). The study authors suggested that the corneal effects resulted from direct radon exposure and plating out of radon progeny on the cornea; thus, effects on both the cornea and lens might be the result of combined external and internal exposures.

No studies were located regarding the following health effects in humans or animals after dermal exposure to radon and radon progeny:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

A statistically significant increase in the incidence of basal cell skin cancers (103.8 observed vs. 13.0 expected) was observed in uranium miners in the Czech Republic who were exposed to radon and

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radon progeny for >10 years (Ševcová et al. 1978). The study authors used the permissible concentration of radon progeny in the workplace air (41,000 MeV/L; approximately equal to 31.9 pCi/L) at the time of the study to calculate a skin contamination of 2.3 ± 0.7 kBq/m² (6.22 pCi/cm²), based on total alpha activity per unit area from the radon progeny, for an experimental group of the miners. Assuming 1,700 working hours per year and using a quality factor of 10 for alpha radiation, the study authors calculated a mean dose equivalent to the basal layer of the epidermis of 60 rem/year. The standard quality factor (now termed radiation weighting factor) for alpha particles is 20, which would yield an equivalent dose of 120 rem/year. Additionally, the study authors noted that during earlier times, concentrations of radon progeny in the uranium mines were up to 10 times higher than the permissible concentration in the late 1970s. Exposure to other agents (such as arsenic, a known dermal carcinogen (see Agency for Toxic Substances and Disease Registry [2007a])) in the uranium mining environment, as well as minor traumas of the skin, may also have contributed to the observed incidence of skin cancer. Increased incidences of skin cancer have not been reported in other uranium miner cohorts or for workers in other types of mining, such as metal or coal mines; these end points were not examined in most of these studies.

Eatough and coworkers performed a series of studies designed to estimate the average dose of alpha radiation from radon and radon progeny to the skin under normal environmental exposure conditions in which airborne particles containing radon and radon progeny make dermal contact (Eatough 1997; Eatough and Henshaw 1992; Eatough et al. 1999). In the study of Eatough et al. (1999), results of personnel monitoring of airborne radon progeny ²¹⁸Po and ²¹⁴Po in which individuals were immersed under normal environmental conditions in the United Kingdom indicated that at the average radon concentration of 20 Bq/m³ (0.54 pCi/L) to continuously exposed skin would result in 3,500–28,000 decays/cm²/year from ²¹⁸Po and 7,000–21,000 decays/cm²/year from ²¹⁴Po. The results of Eatough and coworkers indicate a potential for radon and radon progeny to elicit skin cancer under normal environmental conditions. Few of the alpha particles from those decays would actually reach and expose the dermis since fewer than half would be released toward the body (reducing the values by more than 50%) and most of their energy would transfer to the nonliving epidermis, leaving little to expose the underlying dermis.

No studies were located regarding cancer in animals after dermal exposure to radon and its progeny.

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3.3 GENOTOXICITY

Abundant information is available regarding the genotoxicity of ionizing radiation (refer to the Toxicological Profile for Ionizing Radiation for a detailed discussion of the genotoxic effects of various forms of ionizing radiation). The genotoxicity of alpha radiation from radon and its progeny has been investigated in underground miners, in individuals residing in homes with measured radon levels, in laboratory animals *in vivo*, and in a variety of *in vitro* test systems. Tables 3-6 and 3-7 present the results of *in vivo* and *in vitro* genotoxicity assessments, respectively.

Increases in chromosomal aberrations have been reported in peripheral blood lymphocytes of underground miners exposed to relatively high levels of radon and radon progeny (Bilban and Jakopin 2005; Brandom et al. 1978; Smerhovsky et al. 2001, 2002). Significantly increased frequency of micronuclei was also noted in peripheral blood lymphocytes of lead-zinc miners in the Czech Republic (Bilban and Jakopin 2005). Significantly increased frequency of mutations of glycoporphin A was reported in the blood from a cohort of Radium Hill uranium miners in Australia (Shanahan et al. 1996). The mutation rate tended to increase with increasing radon exposure, with the exception of the most highly exposed group (>10 WLM); there was no clear relation between HPRT mutation rates and previous occupational exposure to radon.

Several studies investigated possible associations between residential exposure to radon and radon progeny and genotoxic end points. Significantly increased frequency of chromosomal aberrations was noted in peripheral blood lymphocytes of a small group of individuals in Germany who resided in homes where radon concentrations were 4–60 times higher than the national average of 50 Bq/m² (Bauchinger et al. 1994). The prevalence of DNA damage in peripheral blood lymphocytes was significantly associated with increased residential radon levels at airborne levels exceeding 200 Bq/m³; no correlation was seen in comparisons of DNA damage to levels of radon in the drinking water for these same individuals, at levels drinking water ranging from 10 to 2,410 Bq/L (Hellman et al. 1999). Results of one small study of 20 individuals indicated a positive association between HPRT mutations in peripheral blood lymphocytes and measured radon levels (Bridges et al. 1991). However, a subsequent assessment by the same investigators using a larger number of exposed subjects (n=66) found no significant positive or negative association between HPRT mutation rates and indoor radon levels (Cole et al. 1996). Radon did not induce increased HPRT mutation rates in another study of a small group (n=11) of residentially-exposed subjects (Albering et al. 1992). No significant increase in the frequency of chromosomal aberrations was

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Table 3-6. Genotoxicity of Radon and Radon Progeny *In Vivo*

| Species (test system) | End point | Results | Reference |
|--------------------------------------|--------------------------------|---------|--|
| Mammalian systems: | | | |
| Human (peripheral blood lymphocytes) | Chromosomal aberrations | + | Bauchinger et al. 1994; Bilban and Jakopin 2005; Brandom et al. 1978; Hellman et al. 1999; Pohl-Rüling and Fischer 1979, 1982; Pohl-Rüling et al. 1976; Smerhovsky et al. 2001, 2002; Stenstrand et al. 1979 |
| Human (peripheral blood lymphocytes) | Chromosomal aberrations | - | Maes et al. 1996 |
| Human (peripheral blood lymphocytes) | Micronuclei | + | Bilban and Jakopin 2005 |
| Human (peripheral blood lymphocytes) | Gene mutations (HPRT) | - | Shanahan et al. 1996 |
| Human (peripheral blood lymphocytes) | Gene mutations (HPRT) | - | Cole et al. 1996 |
| Human (peripheral blood lymphocytes) | Gene mutations (HPRT) | - | Albering et al. 1992 |
| Human (whole blood) | Gene mutations (glycophorin A) | + | Shanahan et al. 1996 |
| Human (lymphocytes) | DNA repair | + | Tuschl et al. 1980 |
| Rat (tracheal epithelial cells) | Chromosomal aberrations | + | Brooks et al. 1992 |
| Rabbit (somatic cells) | Chromosomal aberrations | - | Leonard et al. 1981 |
| Mouse (bone marrow) | Chromosomal aberrations | + | Abo-Elmagd et al. 2008 |
| Rat (alveolar macrophages) | Micronuclei | + | Taya et al. 1994 |
| Rat (lung fibroblasts) | Micronuclei | + | Brooks et al. 1994; Khan et al. 1994, 1995 |
| Syrian hamster (lung fibroblasts) | Micronuclei | + | Khan et al. 1995 |
| Chinese hamster (lung fibroblasts) | Micronuclei | + | Khan et al. 1995 |
| Mouse (red blood cells) | Micronuclei | + | Abo-Elmagd et al. 2008 |
| Rat (bone marrow) | Sister chromatid exchanges | + | Poncy et al. 1980 |

- = negative result; + = positive result

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Table 3-7. Genotoxicity of Radon and Radon Progeny *In Vitro*

| Species (test system) | End point | Result | | Reference |
|-------------------------------------|-------------------------|-----------------|--------------------|---------------------------|
| | | With activation | Without activation | |
| Mammalian cells: | | | | |
| Human (blood lymphocytes) | Chromosomal aberrations | No data | + | Wolff et al. 1991 |
| Human (blood lymphocytes) | Chromosomal aberrations | No data | + | Hamza and Mohankumar 2009 |
| Human (fibroblasts) | Chromosomal aberrations | No data | + | Loucas and Geard 1994 |
| Chinese hamster (ovary AA8 cells) | Chromosomal aberrations | No data | + | Schwartz et al. 1990 |
| Chinese hamster (ovary EM9 cells) | Chromosomal aberrations | No data | + | Schwartz et al. 1990 |
| Chinese hamster (ovary K-1 cells) | Chromosomal aberrations | No data | + | Shadley et al. 1991 |
| Chinese hamster (ovary xrs-5 cells) | Chromosomal aberrations | No data | – | Shadley et al. 1991 |
| Chinese hamster (ovary K-1 cells) | Gene mutations | No data | + | Shadley et al. 1991 |
| Chinese hamster (ovary xrs-5 cells) | Gene mutations | No data | + | Shadley et al. 1991 |
| Chinese hamster (ovary AA8 cells) | Gene mutations | No data | + | Schwartz et al. 1990 |
| Chinese hamster (ovary EM9 cells) | Gene mutations | No data | + | Schwartz et al. 1990 |
| Chinese hamster (ovary C18 cells) | Gene mutations | No data | + | Jostes et al. 1994 |
| Mouse (L5178Y cells) | Gene mutations | No data | + | Evans et al. 1993a, 1993b |

– = negative result; + = positive result

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found in another small group (n=22) of subjects with residential exposure to radon at concentrations in the range of 50–800 Bq/m³ (Maes et al. 1996).

Increases in chromosomal aberrations were reported among spa-house personnel and in area residents in Badgastein, Austria, who were chronically exposed to radon and radon decay products present in the environment (Pohl-Rüling and Fischer 1979, 1982; Pohl-Rüling et al. 1976). A study by Tuschl et al. (1980) indicated a stimulating effect of repeated low-dose *in vitro* ultraviolet or beta irradiation on DNA repair in lymphocytes of persons occupationally exposed to radon (3,000 pCi/L of air [1.1x10⁵ Bq/m³]). The study authors suggested that this “stimulating” effect of either type of radiation might be attributable to induction of de novo synthesis of repair enzymes. They noted that an error-free repair pathway for DNA involving de novo synthesis of proteins had been reported in *Escherichia coli*, and that miners exposed to radon in Badgastein (a community with elevated levels of background radiation) had fewer chromosomal aberrations than the public despite being exposed to more radiation.

An increase in chromosomal aberrations in lymphocytes was observed in 18 Finnish people of different ages chronically exposed to radon in household water at concentrations of 2.9x10⁴–1.2x10⁶ pCi radon/L of water (1.1x10³–4.4x10⁴ Bq/L) compared with people who did not have a history of exposure to high radon levels (Stenstrand et al. 1979). This study also indicated that the frequencies of chromosomal aberrations and multiple chromosomal breaks were more common in older people than in younger people exposed to radon. Although the radon was in household water, it is probable that much of this radon volatilized and was available to be inhaled. Therefore, this route of exposure includes both oral and inhalation routes.

Available *in vivo* animal data generally support the human data. Significantly increased frequency of micronuclei was observed in lung fibroblasts of Wistar rats, Syrian hamsters, and Chinese hamsters that inhaled radon and radon progeny; cumulative exposures were 115–323 WLM for the rats, 126–278 WLM for the Syrian hamsters, and 496 WLM for the Chinese hamsters (Khan et al. 1994, 1995). The Chinese hamsters appeared to be 3 times more sensitive than rats. Significantly increased frequency of chromosomal aberrations was noted in tracheal epithelial cells of F-344/N rats that had inhaled radon and radon progeny at cumulative exposures of 900 or 1,000 WLM (Brooks et al. 1992). Abo-Elmagd et al. (2008) exposed Swiss albino mice to airborne radon from a pitchblende powder source for 5–25 weeks at concentrations resulting in accumulated radon doses in the range of 13.01–65.05 WLM and reported exposure-related increased structural chromosomal aberrations and decreased mitotic index in bone marrow cells and increased micronuclei in red blood cells. Brooks and coworkers (Brooks et al. 1994)

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reported significantly increased frequency of micronuclei in lung fibroblasts of Wistar rats exposed to radon at levels resulting in cumulative exposures ranging from 115 to 320 WLM. Significantly increased frequency of alveolar macrophages with micronuclei was observed in rats exposed to radon and its progeny at levels designed to give cumulative exposures ranging from 120 to 990 WLM (Taya et al. 1994). Evidence of chromosomal aberrations was equivocal in two rabbit studies. Rabbits exposed to high natural background levels of radon (12 WLM) for over 28 months displayed an increased frequency of chromosomal aberrations (Leonard et al. 1981). However, when a similar study was conducted under controlled conditions (10.66 WLM), chromosomal aberrations were not found. According to the authors, the increased chromosomal aberrations in somatic cells of rabbits exposed to natural radiation were mainly due to the gamma radiation from sources other than radon. Exposure of Sprague-Dawley male rats to radon at cumulative doses as low as 100 WLM resulted in an increase in sister chromatid exchanges (SCEs) in bone marrow by 600 days postexposure (Poncy et al. 1980). At 750 days postexposure, the number of SCEs reached 3.21 per cell. The SCEs in the 500 and 3,000 WLM groups reached constant values of 3.61 and 4.13 SCEs per cell. In the high-dose group (6,000 WLM), SCEs continued to increase from 100 to 200 days after exposure, reaching a mean value of 3.5 SCE per cell. In controls, SCEs were constant with age (2.4 per cell).

The genotoxicity of radon and radon progeny has been assessed in a variety of mammalian cells *in vitro*. Chromosomal aberrations were reported in human blood lymphocytes (Hamza and Mohankumar 2009; Wolff et al. 1991) and human fibroblasts (Loucas and Geard 1994). Hamza and Mohankumar (2009) noted increasing frequency of chromosomal aberrations with increasing radon dose (range 0–0.127 Gy and dose rate (range 5.4×10^{-8} – 7.08×10^{-4} Gy/min) for 3-hour exposures. Exposure of Chinese hamster ovary (CHO) cells to the radon daughter, bismuth-212 (^{212}Bi) caused chromosomal aberrations and gene mutations (Schwartz et al. 1990; Shadley et al. 1991). Gene mutations were induced by irradiation of CHO cells with radiation from radon (Jostes et al. 1994). Another study employed an isotope of helium (^4He) to simulate alpha particles from radon progeny and found exposure-induced gene mutations (Jin et al. 1995). Gene mutations were also induced in mouse L5178Y lymphoblasts exposed to alpha radiation from radon (Evans et al. 1993a, 1993b).

3.4 TOXICOKINETICS

In radiation biology, the term *dose* has a specific meaning. Dose refers to the amount of radiation absorbed by the organ or tissue of interest and is expressed in rad (grays). Estimation of this radiation dose to lung tissue or specific cells in the lung from a given exposure to radon and radon progeny is

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accomplished by modeling the sequence of events involved in the inhalation, deposition, clearance, and decay of radon progeny within the lung. While based on the current understanding of lung morphometry and experimental toxicokinetics data on radon and radon progeny, different models make different assumptions about these processes, thereby resulting in different estimates of dose and risk. These models are described in numerous reports including ICRP (1982), NEA/OECD (1983), NCRP (1984a), Bair (1985), James (1987), EPA (1988), and NAS (1988).

The focus of this section is on describing the empirical basis for our understanding of the toxicokinetics of radon. Physiologically-based models of radon toxicokinetics used in radon radiation dosimetry are described in Section 3.4.5. A complete discussion of toxicokinetics of radon as it relates to the development of adverse health effects in exposed populations (e.g., respiratory tract cancer) must consider not only the physical trapping of the attached fraction of radon progeny in the respiratory tract, but also the toxicokinetics of radon progeny, both of which contribute to the internal radiation dose that occurs in association with exposures to radon. While radioactive decay of the short-lived radon progeny, contribute most of the radiation dose to the respiratory tract following exposures to radon, they are sufficiently long-lived, relative to rates of toxicokinetics processes that govern transport and distribution, to exhibit radionuclide-specific toxicokinetics. Rather than providing a detailed review of the toxicokinetics of each element in the uranium and thorium decay chains leading to the production of radon and radon progeny elements (uranium, thorium, radium, astatine, polonium, bismuth, lead, and thallium) in this profile, the reader is referred to relevant literature on the toxicokinetics of the most widely-studied of these elements, including uranium (Agency for Toxic Substances and Disease Registry 2011; ICRP 1995a, 1995b); thorium (Agency for Toxic Substances and Disease Registry 1990b; ICRP 1995a, 1995b); radium (Agency for Toxic Substances and Disease Registry 1990a; ICRP 1992, 1995b); polonium (ICRP 1992, 1995b; NCRP 1980), lead (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1992, 1995b), and thallium (Agency for Toxic Substances and Disease Registry 1992). The longer-term fate of radon progeny in the body will be reflected in the toxicokinetics of longer-lived progeny, which include ^{210}Pb (radioactive half-life of approximately 22.2 years) and ^{206}Pb (stable end product of the ^{222}Rn decay chain). The reader is referred to the Toxicological Profile for Lead (Agency for Toxic Substances and Disease Registry 2007b) for a discussion of the toxicokinetics of lead. A further complication in relating radon toxicokinetics to adverse health effects associated with exposure to radon is that radon progeny are present with radon in the environment and are inhaled or ingested along with radon. Progeny formed in the environment contribute substantially to radiation dose associated with environments that contain radon gas (Kendall and Smith 2002).

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3.4.1 Absorption**3.4.1.1 Inhalation Exposure**

Inhalation exposures to radon deliver the gas and its progeny (e.g., ^{214}Bi , ^{214}Pb , ^{210}Pb , ^{218}Po , and ^{210}Po ; some attached to atmospheric particles and the rest unattached) into the respiratory tract (Marsh and Birchall 2000). Longer-lived radon progeny (e.g., ^{210}Pb and ^{210}Po) contribute little to the radiation dose to lung tissue because they have a greater likelihood of being physically cleared from the lung by mucociliary or cellular transport mechanisms before they can decay and deliver a significant radiation dose.

Progeny aerosol formation involves distinct physical-chemical processes (Butterweck et al. 2002; El-Hussein et al. 1998; Ishikawa et al. 2003b): (1) immediately after formation, progeny react with gases and vapors and form clusters, referred to as *unattached* particles, having diameters of approximately 0.5–3 nm or (2) unattached particles form complexes with other aerosols or particles in air to form *attached* particles, which can undergo hygroscopic growth to achieve diameters ranging from approximately 50 to 1,500 nm. The magnitude of the unattached fraction in inhaled air depends on the concentration and size distribution of aerosols in the ambient environment, and will vary with the exposure conditions (e.g., indoor, outdoor) and activities of the individual (e.g., sleeping, activities that release particulates into the air) (Marsh and Birchall 2000). The sizes and size distributions of attached particles in smoker homes and mines can be approximately the same, while the particle sizes are smaller in nonsmoker residences (HPA 2009). The unattached fraction for typical indoor environments has been estimated to be 5–20% (Porstendörfer 1994, 2001), while EPA assumes 50%. Smoking and other aerosol-generating activities (e.g., vacuum cleaning, cooking, fireplace and circulating fan usage) will increase the attached fraction, which correspondingly increases the dose (Sun 2008).

Deposition and the subsequent absorption of inhaled radon and radioactive decay progeny are influenced by physiological factors as well as chemical and physical characteristics of the radionuclides, carrier aerosols, and atmospheric particles. Radon is a nonreactive noble gas, and deposition and absorption will be determined by Brownian motion, its solubility in lung fluids, its permeability at the lung:circulating blood interface, and blood flow to the lungs. The blood:air partition coefficient for radon has been estimated to be approximately 0.4 (Nussbaum and Hursh 1957; Sharma et al. 1997); therefore, at steady-state, the blood concentration of radon will be approximately 0.4 times the concentration of radon in lung air. Assuming rapid (i.e., near-instantaneous) partitioning of radon between air and blood, the absorption clearance of radon gas from air in the lung will be governed by the blood flow to the lung (i.e., absorption

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rate will be flow-limited). At a blood flow to the lung of 5.3 L/minute in an adult, and lung air volume of 2.82 L, the $t_{1/2}$ for absorption of radon from lung to blood would be approximately 0.4 min (rate constant=113 hours⁻¹) (Peterman and Perkins 1988). A similar value was estimated for the $t_{1/2}$ for clearance of radon gas from the lung air to external air ($t_{1/2}$ =0.4 minute; rate constant=115 hours⁻¹) (Peterman and Perkins 1988). Rapid clearance of radon gas from the lung by absorption and exhalation will result in steady-state concentrations of radon in blood within 2–3 minutes of initiating exposure to radon gas. Clearance of radon from the blood following removal from exposure will be governed by blood flow rates to major tissue depots for radon (see Section 3.4.2).

Exposures to radon in air occur along with exposures to aerosols of radon progeny, which will deposit on the lung epithelia. The amounts and location of deposition of radon progeny will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. These factors include air flow velocities, which are affected by breathing rate and tidal volume; airway geometry; and aerosol particle size (Cohen 1996; James et al. 1994; Kinsara et al. 1995; Marsh and Birchall 2000; Yu et al. 2006). Radon progeny consist of a mixed distribution of unattached and attached particles. Assuming activity median aerodynamic diameters (AMAD) of approximately 1–3 nm for the unattached fraction and 100–200 nm for attached particles (Butterweck et al. 2002; Ishikawa et al. 2003b), deposition fractions of inhaled radon progeny can be estimated from models of particle deposition in the human respiratory tract (ICRP 1994b). The deposition fraction (i.e., percent of total number of inhaled particles that deposit) for unattached particles is predicted to be approximately 97–99%, with most of the deposition (70–80%) occurring in the extrathoracic region of the respiratory tract. The deposition fraction for attached particles is predicted to be approximately 20–40% with most of the deposition occurring in the alveolar region. Deposition will occur more predominantly in the nasal airways when breathing occurs through the nose. These predictions are based on the ICRP (1994b) human respiratory tract model assuming recommended values for deposition fractions for adult members of the general public exposed to homogeneous aerosols, and will vary with different assumptions for breathing rate and ratio of nose-to-mouth breathing (ICRP 2001). Predictions that deposition will be higher for the unattached fraction compared to the attached fraction and higher for nose-breathing exposures are in reasonable agreement with experiments conducted in humans exposed to heterogeneous distributions of aerosols of radon progeny (Booker et al. 1969; George and Breslin 1967, 1969; Holleman et al. 1969; Hursh and Mercer 1970; Hursh et al. 1969a; Ishikawa et al. 2003b; Pillai et al. 1994; Swift and Strong 1996) and with experiments conducted using casts of the human respiratory tract (Chamberlain and Dyson 1956; Cohen 1996; Kinsara et al. 1995; Martin and Jacobi 1972). The deposition fraction in subjects who inhaled (nose-only) 0.5–0.6-nm particles of ²¹⁸Po was estimated to be

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approximately 94–99% (Swift and Strong 1996). Near complete deposition (>99%) was observed in an adult subject who inhaled (mouth-only) unattached particles of ^{212}Pb formed from decay of ^{220}Rn in a low ambient aerosol environment, whereas the deposition fraction was 34–60% when the exposure was to aerosols formed in room air and having a particle size range of 50–500 nm, more typical of attached particles (Booker et al. 1969). Deposition fractions for radon progeny have been measured during exposures to aerosols in underground uranium mines (George and Breslin 1969; Holleman et al. 1969). Deposition fractions increased with increasing tidal volume, and decreased with increasing aerosol aerodynamic diameter, from 50–70% for diameters <10 nm to 30–40% for diameters >70 nm. Hursh and Mercer (1970) estimated thoracic deposition (i.e., total of bronchi, bronchioles, and alveolar region) based on external gamma counting of the chest area of ^{212}Pb produced from decay of ^{220}Rn and inhaled (mouth-only) as aerosols having AMADs of 20–25 or 200–230 nm. The deposition fractions in adult subjects were approximately 50–62% for the smaller particles and 27–38% for the larger particles. When adult subjects inhaled (mouth-only) natural ^{212}Pb aerosols generated from ^{220}Rn decay in room air, the measured deposition fractions ranged from 14–45% (Hursh et al. 1969a). Pillai et al. (1994) made chest gamma measurements on four subjects who were exposed to ^{212}Pb aerosols for 10–60 minutes in a thorium hydroxide storage facility. The particle size of the ^{212}Pb aerosol was approximately 90 nm. Deposition fraction was estimated to have been 55–76%.

Particles containing radon progeny that deposit in the respiratory tract are subject to three general clearance processes: (1) mucociliary transport to the gastrointestinal tract for progeny deposited in the ciliated airways (i.e., trachea, bronchi, and bronchioles); (2) phagocytosis by lung macrophages and cellular transport to lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption and transfer by blood and/or lymph to other tissues. The above processes apply to all forms of deposited radon progeny, although the relative contributions of each pathway and rates associated with each pathway may vary with the physical characteristics (e.g., particle size), chemical form (degree of water solubility), and radiological characteristics (e.g., specific activity).

Absorption half-times ($t_{1/2}$) have been estimated for radon decay progeny in adults who inhaled aerosols of lead and bismuth isotopes generated from decay of ^{220}Rn or ^{222}Rn . Values for ^{212}Pb and ^{212}Bi in an aerosol having an activity median particle diameter of approximately 160 nm (range 50–500 nm), a value typical of attached radon progeny particles, were estimated to be approximately 10 and 13 hours, respectively (Marsh and Birchall 1999). The latter estimates were based on an analysis of data from human inhalation exposures to ^{212}Pb and ^{212}Bi progeny of ^{220}Rn (Booker et al. 1969; Hursh and Mercer 1970; Hursh et al. 1969a; Jacobi 1964; Pillai et al. 1994). However, absorption of unattached radon

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progeny may be faster than that of attached progeny. Butterweck et al. (2002) exposed nose- or mouth-breathing human subjects to ^{222}Rn -derived aerosols that had diameters of approximately 0.3–3 nm, typical of unattached progeny particles. Absorption half-times were estimated to be approximately 68 minutes (range 56–86) for $^{218}\text{Po}/^{214}\text{Pb}$ and 18 minutes (range 17–21) for ^{214}Bi . Binding of unattached radon progeny in the respiratory tract may result in slower absorption kinetics. Butterweck et al. (2002) proposed that a 10-hour $t_{1/2}$ would apply to the unattached fraction after binding in the respiratory tract, and that the unbound fraction may have an absorption $t_{1/2} < 10$ minutes. This behavior would be consistent with dissolution of deposited particles being the rate-limiting step in absorption and smaller particles dissolving faster than larger particles.

3.4.1.2 Oral Exposure

Exposure to radon by the oral route can occur as a result of radon gas dissolving in water. At equilibrium, the concentration of radon dissolved in water will be approximately 0.25 of that in air (i.e., Henry's law constant=4.08 at 20 °C) (NAS 1999b). Radioactive decay of radon in water produces radon progeny; therefore, ingestion of water containing dissolved radon will also result in ingestion of radon progeny. Absorption of radon is thought to occur primarily in the stomach and small intestine, although some absorption may also occur in the large intestine (Ishikawa et al. 2003a; Khursheed 2000; NAS 1999b). Radon is relatively nonreactive and its absorption from the stomach will be determined largely by rates of diffusion of radon from stomach contents to vascularized mucosa; its solubility in the stomach tissues and blood; blood flow to the stomach; and rates of transfer of stomach contents into the intestine (Ishikawa et al. 2003a; NAS 1999b). Diffusion of radon from stomach contents to stomach tissues may be rate-limiting in absorption (NAS 1999b). However, assuming rapid (i.e., near-instantaneous) partitioning of radon from vascularized mucosa to blood, the absorption clearance of radon from stomach mucosa will be governed by the blood flow rate to the stomach (i.e., absorption rate will be flow-limited). At a stomach blood flow of 1% of cardiac output (1% of 6.5 L/minute in an adult), and stomach wall volume of approximately 0.15 L (NAS 1999b), the $t_{1/2}$ for absorption of radon from the stomach wall to blood would be approximately 1.6 minutes (rate constant=0.43 minute^{-1}). An absorption $t_{1/2}$ of 1–2 minutes is consistent with observations of peak blood radon concentrations and peak radon concentrations in exhaled air within 5 minutes following ingestion of radon in water by adults (Brown and Hess 1992; Hursh et al. 1965; Sharma et al. 1997).

Kinetics of absorption of radon progeny are more complex, reflecting different mechanisms (e.g., membrane cation transport proteins and channels) and sites of absorption for radon and progeny.

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Absorption of radon progeny following oral exposure is thought to occur largely in the small intestine (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1994c). As a result, absorption of ingested progeny, and progeny formed from radon after ingestion, will be influenced by rates of transfer of stomach contents into the small intestine, as well as rates of absorption of progeny from the small intestine. Ishikawa et al. (2003a) used external gamma counting to measure the kinetics of elimination of ^{214}Pb and ^{214}Bi from the stomach following ingestion of water containing radon. Elimination kinetics from the stomach exhibited multiple components, with a fast phase (40–50% of ingested activity) having a $t_{1/2}$ value of approximately 10 minutes and two slower phases having $t_{1/2}$ values of 150 and 240 minutes. The presence of food in the stomach delays stomach emptying and may alter the absorption kinetics of radon and progeny (Brown and Hess 1992; Hursh et al. 1965; Suomela and Kahlos 1972). ICRP (1995c, 2001) recommends values of 0.05 and 0.1 as gastrointestinal absorption fractions for bismuth and polonium, respectively. The absorption fraction for ingested inorganic lead varies with age; from 40 to 50% in infants and children to approximately 8–15% in adults (Agency for Toxic Substances and Disease Registry 2007b; Leggett 1993; O’Flaherty 1993).

3.4.1.3 Dermal Exposure

Data regarding the absorption of radon following dermal exposure are very limited. Dermal absorption of radon has been measured in subjects after bathing in a radon-water spa (Furuno 1979; Pohl 1965) or after application of a radon-containing ointment to the intact skin (Lange and Evans 1947). After bathing for 5–15 minutes, radon concentrations in expired air reached approximately 0.9% of that in the water and ranged from 17.9 to 49.1 pCi/L of air (662–1,817 Bq/m³) compared to pre-bath levels of <1 pCi/L of air (37 Bq/m³). Radon concentrations in the water were reported by the authors as 5,800 pCi (215 Bq)/kg. However, the relative contributions of the dermal and inhalation routes of absorption cannot be determined in these studies (Furuno 1979). Radon concentrations in blood reached 0.85–1% of the radon concentration in the bath water, which was 1.8×10^5 pCi (4.9×10^6 Bq)/L of water after 30–40 minutes of bathing while breathing compressed air (Pohl 1965). Approximately 4.5% of the radon applied in ointment to intact skin was measured in expired air within 24 hours following application (Lange and Evans 1947).

Peterman and Perkins (1988) proposed a model for simulating the absorption of radon, based on a model largely parameterized to simulate absorption of xenon gas through the skin. Although parameter values for radon were not reported and skin penetration of radon was not modeled, the general structure is potentially relevant to estimating radon absorption rates. In the Peterman and Perkins (1988) model, the

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rate-limiting step in dermal absorption was considered to be the diffusion of xenon through the skin to the subcutaneous fat. Transfer from subcutaneous fat to blood was assumed to be flow-limited and determined by blood flow to subcutaneous fat. Peterman and Perkins (1988) estimated the dermal diffusion rate of xenon to be approximately 0.18 hour^{-1} . This rate would be equivalent to a $t_{1/2}$ value of approximately 4 hours and is substantially slower than the $t_{1/2}$ for absorption from lung ($t_{1/2}=0.4$ minutes; rate constant= 115 hours^{-1}) (Peterman and Perkins 1988). The corresponding $t_{1/2}$ value for absorption from subcutaneous fat was approximately 38 minutes (rate= $0.018 \text{ minute}^{-1}$), assuming a blood flow of 0.16 L/minute and a tissue volume of 8.2 L.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Based on studies conducted in animals, the distribution of absorbed radon appears to reflect its solubility in water and fat. Nussbaum and Hursh (1957) exposed rats to radon gas in an enclosed exposure chamber (whole body) for periods of 30 minutes to 48 hours and measured tissue radon levels at the conclusion of the exposure. The highest radon concentrations were observed in fat. Tissue:air concentration ratios were as follows (mean \pm standard error [SE]): omental fat 4.83 ± 0.07 , venous blood 0.405 ± 0.016 , brain 0.309 ± 0.008 , liver 0.306 ± 0.004 , kidney 0.285 ± 0.012 , heart 0.221 ± 0.013 , testis 0.184 ± 0.007 , and skeletal muscle 0.154 ± 0.005 . Tissue:air ratios for soft tissues reported by Nussbaum and Hursh (1957) are close to those expected for a Henry's law constant of 4 (i.e., water:air=0.25) and a lipid:air partition coefficient of 6 (Nussbaum and Hursh 1957). For example, assuming fat and water contents of soft tissue of 5 and 70%, respectively, in the rat (Davies and Morris 1993), the tissue:air ratio for soft tissue would be approximately 0.36 if solubility in water and fat were the only determinants of tissue radon levels. The corresponding fat:air ratio would be 5.85 for a lipid content of adipose tissue of 80% and water content of 15%. The tissue:air ratios reported in Nussbaum and Hursh (1957) are the bases of tissue:blood partition coefficients that have been used in various biokinetics models (e.g., Khursheed 2000; NAS 1999b; Peterman and Perkins 1988; Sharma et al. 1997).

Nussbaum and Hursh (1957) also reported information on the kinetics of uptake of inhaled radon in tissues. In all tissues studied, except fat, steady-state levels of radon were achieved within 1 hour of initiating a continuous inhalation exposure. Uptake into omental fat was slower and exhibited fast and slow components having $t_{1/2}$ values of 21 and 138 minutes, respectively. The slower uptake kinetics of fat may reflect, in part, the relatively slower blood perfusion of adipose tissue (per unit mass of tissue)

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compared to other soft tissues. Similarly, relatively slow perfusion of fat should contribute a slower component to total body elimination kinetics following cessation of exposure to radon (see Section 3.4.3).

Information about the distribution of absorbed radon progeny, bismuth, lead, and polonium can be found in reviews of these subjects (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 1995c). A relatively large fraction of inhaled ^{212}Pb (inhaled as natural ^{212}Pb aerosols generated from ^{220}Rn decay in room air) distributes to red blood cells (Booker et al. 1969; Hursh et al. 1969a). Red cell ^{212}Pb burdens, expressed as percent of the lead initially deposited in the respiratory tract, increased from approximately 5% within 1–2 hours following exposure to approximately 50% at times >24 hours following exposure (Hursh et al. 1969a). Long-lived (^{210}Pb) and stable progeny (^{206}Pb , ^{207}Pb , and ^{208}Pb), can be expected to deposit and be retained in bone, where approximately 90% of the total lead body burden resides (Agency for Toxic Substances and Disease Registry 2007b). Following chronic exposure in humans, ^{210}Pb has been found in bone (Black et al. 1968; Blanchard et al. 1969; Cohen et al. 1973; Fry et al. 1983) and teeth (Clemente et al. 1982, 1984). ICRP (1980, 2001) recommends, for the purpose of modeling bismuth-derived radiation doses, that 40% of absorbed bismuth distributes to kidneys and 30% to other tissues; the remaining 30% is assumed to be excreted rapidly and does not contribute to distribution beyond the central compartment. Retention in kidneys and other tissues are assumed to be the same (elimination $t_{1/2}$ values of 0.6 and 5 days for fast and slow phases); therefore, approximately 40% of the body burden of bismuth would be in the kidneys. ICRP (1994c, 2001) recommends the following values for percentages of absorbed polonium distributed to tissues: 30% liver, 10% kidney, 10% red marrow, 5% spleen, and 45% other tissues. Retention in all tissues is assumed to be the same (elimination $t_{1/2}$ =50 days); therefore, the latter percent distributions will reflect the distribution of the body burden of polonium (e.g., 30% in liver).

3.4.2.2 Oral Exposure

Measurements of the tissue distribution of radon or progeny following ingestion of radon have not been reported. However, as discussed in Section 3.4.2.1, the distribution of absorbed radon appears to reflect its solubility in water and fat; therefore, steady-state distribution following absorption from the gastrointestinal tract would be determined by tissue:blood partition coefficients and the rate of approach to steady state would be determined by tissue blood flows. Based on tissue:air ratios reported by Nussbaum and Hursh (1957) during inhalation exposures of rats (see Section 3.4.2.1 for further discussion), the following tissue:blood ratios (i.e., tissue:blood=tissue:air/blood:air) can be estimated for

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radon in the rat: omental fat 12, brain 0.76, liver 0.76, kidney 0.70, heart 0.55, testes 0.45, and skeletal muscle 0.38. Therefore, the highest concentrations of radon would be predicted for adipose tissues.

Distribution of absorbed radon progeny would be expected to be similar to the distribution following inhalation exposures, although, first-pass delivery to the liver from the gastrointestinal tract may influence the tissue distribution. As discussed in Section 3.4.2.1, the largest fractions of the body burdens for radon progeny would be expected to be found in bone for lead, kidney for bismuth, and liver for polonium (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 2001).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans or laboratory animals after dermal exposure to radon or its progeny. However, as discussed in Sections 3.4.2.1 and 3.4.2.2, the distribution of absorbed radon appears to reflect its solubility in water and fat; therefore, steady-state distribution following absorption from the skin would be determined by tissue:blood partition coefficients and the rate of approach to steady state would be determined by tissue blood flows.

3.4.3 Metabolism

Radon is an inert noble gas that does not interact chemically with cellular macromolecules. Radon does not undergo metabolism in biological systems.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Measurements of exhaled radon following ingestion of radon dissolved in water indicate that absorbed radon is rapidly excreted in exhaled air (see Section 3.4.4.2). Inhaled ^{212}Pb is excreted in urine and feces. Hursh et al. (1969a) estimated that, following inhalation of natural ^{212}Pb aerosols generated from ^{220}Rn decay in room air, 3% of the amount initially deposited in the respiratory tract was excreted in urine per day and approximately 3%/day was excreted in feces. Longer-term kinetics of excretion of ^{210}Pb following chronic exposures to radon progeny may be contributed from slow release of ^{210}Pb accumulated in bone (Black et al. 1968). Additional information on the elimination of inhaled radon progeny can be found in reviews of the biokinetics of bismuth, lead, and polonium (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 2001). ICRP (1995c, 2001) recommends the following values for the purpose of modeling bismuth-derived radiation doses: a urine:fecal excretion ratio of 1:1

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and elimination $t_{1/2}$ values of 0.6 (60% of tissue burden) and 5 days (40% of tissue burden) for fast and slow phases, respectively. ICRP (1995c, 2001) recommends the following values for elimination of polonium from tissues into urine and feces: a urine:fecal excretion ratio of 1:2 and an elimination $t_{1/2}$ value of 50 days.

3.4.4.2 Oral Exposure

Measurements of exhaled radon following ingestion of radon dissolved in water indicate that exhaled air is the dominant route of excretion of ingested radon (Brown and Hess 1992; Gosink et al. 1990; Hursh et al. 1965). Biological elimination kinetics of absorbed radon in exhaled air exhibit multiple phases, with the first half-time ranging from 15 to 80 minutes (Brown and Hess 1992; Gosink et al. 1990; Hursh et al. 1965). Hursh et al. (1965) estimated the following $t_{1/2}$ values for fast, moderate and slow phases of biological elimination: approximately 13 minutes (61% of body burden), 19 minutes (34%), and 207 minutes (5%), respectively; 95% of the dose was eliminated within 100 minutes. The slow phase of elimination is consistent with observations made in rats of relatively slow accumulation of radon in adipose tissue during continuous inhalation exposures to radon (Nussbaum and Hursh 1957). The latter $t_{1/2}$ values were estimated for subjects who ingested radon in water during fasting. In a subject who ingested radon in water with a meal, moderate and slow phases of elimination appeared to be delayed, with approximate $t_{1/2}$ values of 12 minutes (39% of body burden), 60 minutes (51%), and 300 minutes (10%), respectively. Slowing of elimination when radon is ingested with a meal or with lipid has been observed in several studies and may be related to a delay in stomach emptying that alters the absorption kinetics of radon and progeny (Brown and Hess 1992; Hursh et al. 1965; Meyer 1937; Suomela and Kahlos 1972; Vaternahm 1922).

Suomela and Kahlos (1972) estimated radon elimination kinetics in adults who ingested radon in water by monitoring external gamma-radiation from ^{214}Bi (i.e., assuming $^{214}\text{Bi}:^{222}\text{Rn}$ disequilibrium ratios ranging from 0.4 to 1). Biological elimination $t_{1/2}$ values ranged from 30 to 50 minutes; these are consistent with estimates based on exhaled radon as described above. Out of 10 subjects, ^{214}Bi was detected in urine in two subjects (0.4 and 1.8% of ingested ^{214}Bi dose; duration of urine collection was not reported).

Additional information on the elimination of ingested radon progeny can be found in reviews of the biokinetics of bismuth, lead, and polonium (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 2001). In general, the rates and routes of elimination of each progeny absorbed from the gastrointestinal and respiratory tracts are likely to be similar. Information on elimination of inhaled radon progeny is discussed in Section 3.4.4.1.

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3.4.4.3 Dermal Exposure

Information on the excretion of radon and its progeny following dermal exposure is very limited. Within 24 hours, 4.5% of the radon, which was applied as a salve to intact human skin, was eliminated by exhalation, while 10% was exhaled after application of the radon to an open wound (Lange and Evans 1947). Bathers breathing compressed air while immersed in radon-containing water had exhaled approximately one-third of radon measured in blood immediately after bathing (Pohl 1965). By 6–8 minutes after bathing, these persons were exhaling one-half of the amounts exhaled immediately after bathing. The author stated that the remaining radon which distributed to fatty tissue was excreted more slowly.

3.4.4.4 Other Routes of Exposure

Experiments in animals have reported the retention of radon after exposure by the intraperitoneal and intravenous routes. Following intravenous administration, 1.6–5.0% of the administered activity was retained in the animals after 120 minutes (Hollcroft and Lorenz 1949). Retention was greatest at 120 minutes following intraperitoneal administration, but by 240 minutes, it was nearly the same for both routes of administration. These authors also reported that the amount of radon retained in tissues was greater in obese mice than in normal mice, especially after intraperitoneal administration (Hollcroft and Lorenz 1949). Radon retention has also been studied in dogs following intravenous administration of ^{226}Ra . The amount of radon in bone was found to increase with increasing time after injection (Mays et al. 1975).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

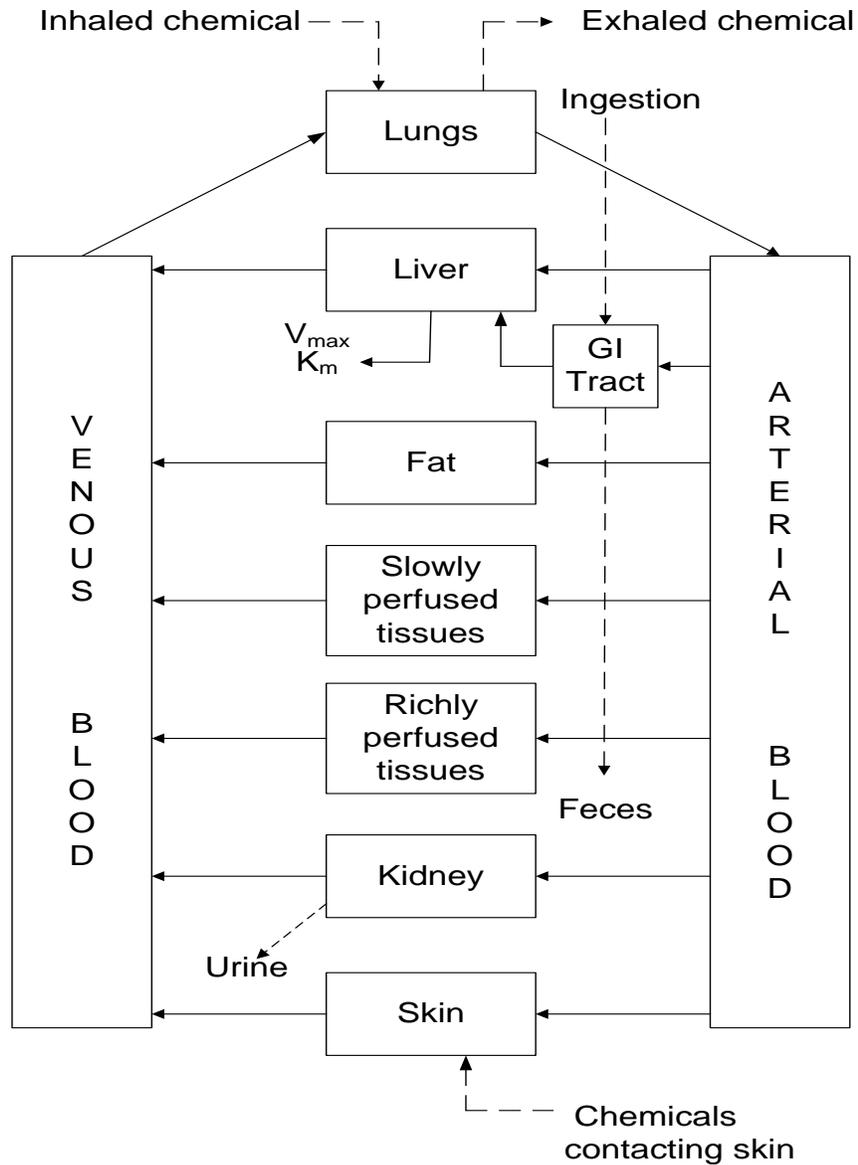
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-2 shows a conceptualized representation of a PBPK model.

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Figure 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

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PBPK models for radon are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. For radionuclides, the PBPK model depicted in Figure 3-2 is replaced with a set of physiologically based biokinetic (PBBK) models for inhalation, ingestion, and submersion. These were developed to accomplish virtually the same end as the PBPK models above, while integrating additional parameters (for radioactive decay, particle and photon transport, and compound-specific factors). Goals are to facilitate interpreting chest monitoring and bioassay data, assessing risk, and calculating radiation doses to a variety of tissues throughout the body. The standard for these models has been set by the ICRP, and their models receive international support and acceptance. ICRP periodically considers newer science in a type of weight of evidence approach toward improving the state of knowledge and reducing uncertainties associated with applying the model to any given radionuclide. ICRP publications also allow for the use of situation- and individual-specific data to reduce the overall uncertainty in the results. Even though there may be conflicting data for some parameters, such as absorption factors, one can use conservative values and still reach conclusions on whether the dose is below recommended limits. One of the strengths of the ICRP model is that it permits the use of experimentally determined material-specific absorption parameter values rather than requiring the use of those provided for default types. If the material of interest does not include absorption parameter values that correspond to those in the model (e.g., Type F, M, or S), the difference can have a profound effect on the assessment of intake and dose from bioassay measurements. This has been discussed in National Radiological Protection Board (NRPB) published reports on uranium (NRPB 2002).

The ICRP (1994b, 1996a) developed a Human Respiratory Tract Model for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to particulate aerosols and gases. The National Council on Radiation Protection and Measurements (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating exposures for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; Deposition, Retention and Dosimetry of Inhaled Radioactive Substances (NCRP 1997).

Models to estimate radiation doses from inhalation exposures to radon account for the deposition and clearance of radon gas as well as aerosols of radon progeny (Yu et al. 2006). Several radiation dose models for inhaled and/or ingested radon gas and progeny in humans have been reported (Birchall and James 1994; Crawford-Brown 1989; El-Hussein et al. 1998; Harley and Robbins 1994; Ishikawa et al. 2003a, 2003b; James et al. 2004; Khursheed 2000; Marsh and Birchall 2000; NAS 1999b; Peterman and Perkins 1988; Porstendörfer, 2001; Sharma et al. 1997). Some of these are extensions or modifications of

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the ICRP (1994b) model that simulates deposition, clearance, and absorption of inhaled gaseous and particulate radionuclides in the human respiratory tract. An example of the latter is the Radon Dose Evaluation Program (RADEP), which has been used extensively in risk assessment of exposures to radon and radon progeny (Birchall and James 1994; Marsh and Birchall 2000). Two other extensions of the ICRP (1994b) model that have been widely applied to radon radiation risk assessment are those of Porstendörfer (2001) and James et al. (2004), which implement different approaches to the simulation of attached and unattached particles (e.g., fractional distributions in inhaled air and hygroscopic growth) and/or effective radiation dose calculations (e.g., tissue weighting factors for radon progeny in respiratory tract tissues). The structure of the biokinetics portion of the generic ICRP human respiratory tract model is described below, along with modifications that have been reported for applications to radon (e.g., RADEP). Systemic distribution and excretion of radon progeny are simulated with models specific for the progeny radionuclides. Descriptions of ICRP models for bismuth, lead, and polonium are reported elsewhere (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1979, 1994c, 1995c; Leggett 1993).

Most physiologically based models of radon biokinetics simulate radon transfers between tissues and blood as flow-limited processes in which clearance is determined by tissue blood flow and tissue concentrations are defined by tissue:blood partition coefficients (Crawford-Brown 1989; Harley and Robbins 1994; Khursheed 2000; NAS 1999b; Peterman and Perkins 1988; Sharma et al. 1997). The model proposed by Peterman and Perkins (1988) was actually developed to simulate noble gases (e.g., xenon); however, it has been applied to radon biokinetics (Peterman and Perkins 1988; Sharma et al. 1997). A unique feature of the model is that it included parameters for simulating absorption of xenon gas through the skin, although parameter values for radon were not reported and skin penetration of radon was not modeled (see Section 3.4.1.3 for discussion of possible implications of this model for dermal absorption of radon). The NAS (1999b) and Khursheed (2000) models are described below as examples of flow-limited models that simulate absorption, distribution, and excretion of inhaled or ingested radon gas. Both were developed to be used in conjunction with ICRP models of progeny to simulate radiation doses from inhalation or ingestion of radon gas in drinking water.

Human Respiratory Tract Model for Radiological Protection (ICRP 1994b)

Deposition. The ICRP (1994b) has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region of the respiratory tract. ICRP (1994b) provides information used in

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calculating effective doses of radiation to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values that can be adjusted for various segments of the population (e.g., sex, age, and level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. The model has been used for estimating radiation doses from inhalation of radon gas and aerosols of radon progeny; however, it was developed to be applied to a wide variety of radionuclides and their chemical and physical forms.

The ICRP deposition model estimates the fraction of inhaled material initially retained in each compartment (see Figure 3-3). The model was developed with five compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

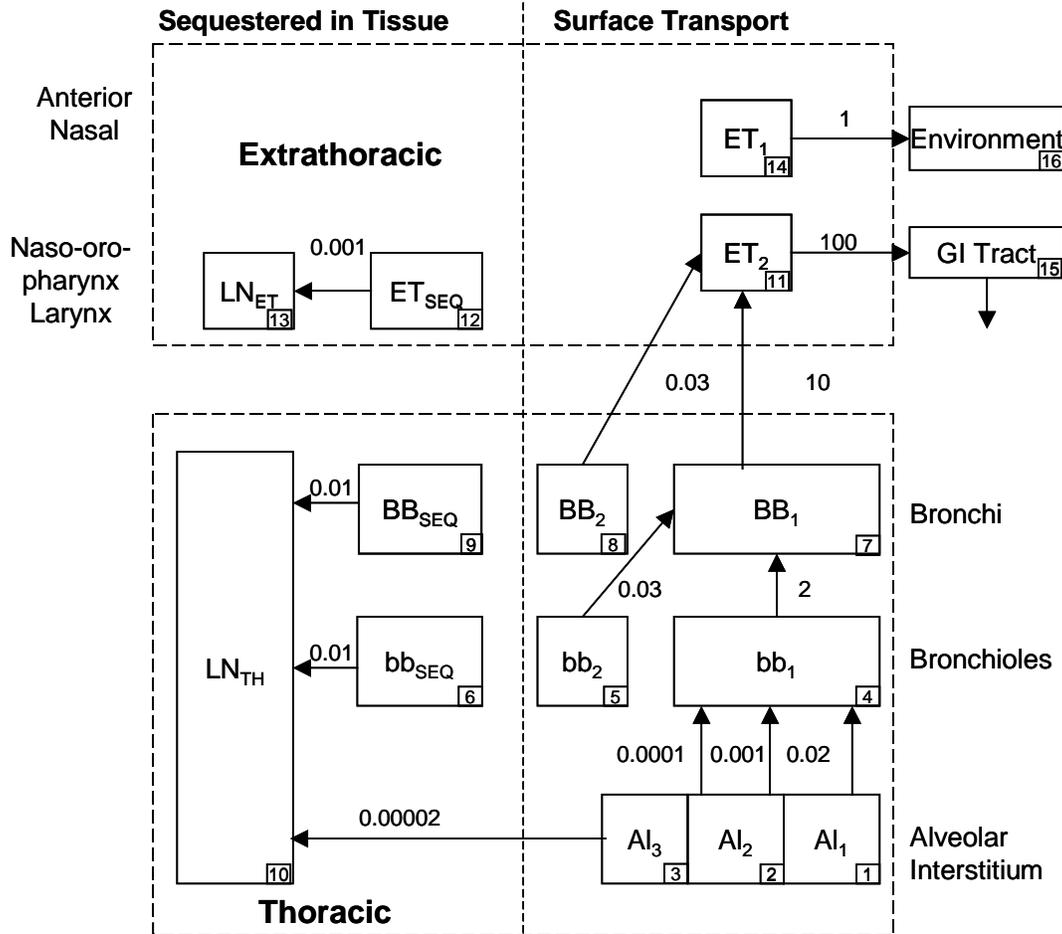
For extrathoracic deposition of particles, the model uses measured airway diameters and experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similar to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-8 provides reference respiratory values for the general Caucasian population during various intensities of physical exertion.

Deposition of inhaled gases and vapors is modeled as a partitioning process that depends on the physiological parameters noted above as well as the solubility and reactivity of a compound in the respiratory tract (see Figure 3-4). The ICRP (1994b) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H_2 , He). These compounds do not significantly interact with the respiratory tract tissues, and essentially all compound inhaled is exhaled. Radiation doses from inhalation exposure of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

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Figure 3-3. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-9.

Source: ICRP 1994b

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Table 3-8. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

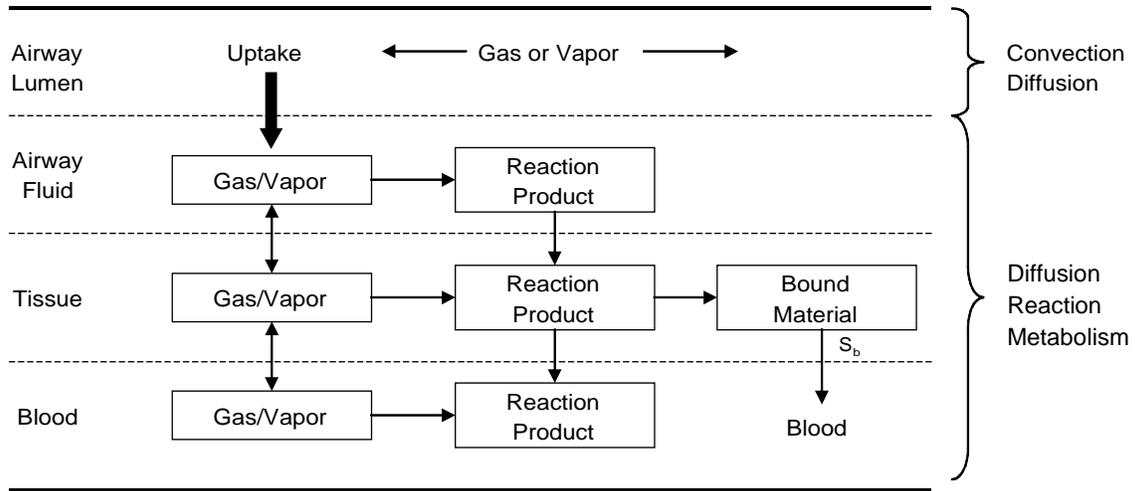
| Breathing parameters: | 3 Months | 1 Year | 5 Years | 10 Years | | | 15 Years | | Adult | |
|---|----------|--------|---------|----------|--------|------|----------|--------|-------|--------|
| | | | | Male | Female | Both | Male | Female | Male | Female |
| Resting (sleeping); maximal workload 8% | | | | | | | | | | |
| Breathing parameters: | | | | | | | | | | |
| $V_T(L)$ | 0.04 | 0.07 | 0.17 | — | — | 0.3 | 0.500 | 0.417 | 0.625 | 0.444 |
| $B(m^3hour^{-1})$ | 0.09 | 0.15 | 0.24 | — | — | 0.31 | 0.42 | 0.35 | 0.45 | 0.32 |
| $f_R(minute^{-1})$ | 38 | 34 | 23 | — | — | 17 | 14 | 14 | 12 | 12 |
| Sitting awake; maximal workload 12% | | | | | | | | | | |
| Breathing parameters: | | | | | | | | | | |
| $V_T(L)$ | NA | 0.1 | 0.21 | — | — | 0.33 | 0.533 | 0.417 | 0.750 | 0.464 |
| $B(m^3hour^{-1})$ | NA | 0.22 | 0.32 | — | — | 0.38 | 0.48 | 0.40 | 0.54 | 0.39 |
| $f_R(minute^{-1})$ | NA | 36 | 25 | — | — | 19 | 15 | 16 | 12 | 14 |
| Light exercise; maximal workload 32% | | | | | | | | | | |
| Breathing parameters: | | | | | | | | | | |
| $V_T(L)$ | 0.07 | 0.13 | 0.24 | — | — | 0.58 | 1.0 | 0.903 | 1.25 | 0.992 |
| $B(m^3hour^{-1})$ | 0.19 | 0.35 | 0.57 | — | — | 1.12 | 1.38 | 1.30 | 1.5 | 1.25 |
| $f_R(minute^{-1})$ | 48 | 46 | 39 | — | — | 32 | 23 | 24 | 20 | 21 |
| Heavy exercise; maximal workload 64% | | | | | | | | | | |
| Breathing parameters: | | | | | | | | | | |
| $V_T(L)$ | NA | NA | NA | 0.841 | 0.667 | — | 1.352 | 1.127 | 1.923 | 1.364 |
| $B(m^3hour^{-1})$ | NA | NA | NA | 2.22 | 1.84 | — | 2.92 | 2.57 | 3.0 | 2.7 |
| $f_R(minute^{-1})$ | NA | NA | NA | 44 | 46 | — | 36 | 38 | 26 | 33 |

B = ventilation rate; f_R = respiration frequency; NA = not applicable; V_T = tidal volume

Source: See Annex B (ICRP 1994b) for data from which these reference values were derived.

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Figure 3-4. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



Source: ICRP 1994b

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- Type SR-1 compounds include soluble or reactive gases and vapors which are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound.
- Type SR-2 compounds include soluble and reactive gases and vapors which are completely retained in the extrathoracic regions of the respiratory tract. SR-2 compounds include sulfur dioxide (SO₂) and hydrogen fluoride (HF).

Radon gas is categorized by ICRP (1994b) as SR-1, because, even though it has a low reactivity, it is sufficiently soluble to be taken up in the alveolar region where it can be absorbed into blood. ICRP (1994b) recommended default values for regional distribution of inhaled gases (except for those having low solubility) as follows: 10% ET₁, 20% ET₂, 10% BB, 20% bb, and 40% AI. Radon progeny, such as ²¹⁸Po, ²¹⁴Pb, and ²¹⁴Bi are sufficiently reactive to attach to aerosols in the respiratory tract (and external air) and deposit in the respiratory tract according to factors that determine particulate deposition (e.g., sedimentation, inertial impaction, diffusion, and interception). Radon progeny are represented in the ICRP (1994b) model and in extensions of the model (e.g., RADEP) as a mixed distribution of unattached particles (i.e., products of the initial reactions between progeny with gases and vapors) and attached particles (i.e., products of hygroscopic growth of complexes between unattached particles and aerosols in air). AMADs for the two fractions are typically represented in the ICRP model as 1 nm for unattached particles and 200 nm for attached particles (Butterweck et al. 2002; Ishikawa et al. 2003b), although the use of more complex mixed distributions for attached particles has also been used (Marsh and Birchall 2000; Porstendörfer 1994, 2001).

The magnitude of the unattached fraction in inhaled air depends on the concentration and size distribution of aerosols in the ambient environment, and will vary with the exposure conditions (e.g., indoor, outdoor) and activities of the individual (e.g., sleeping, activities that release particulates into the air such as smoking) (Marsh and Birchall 2000). The unattached fraction for typical indoor environments has been estimated to be 5–20% (Porstendörfer 1994, 2001). NRC (1991) recommended a default value of 3% for modeling exposures in homes where smoking occurs and 5% for exposures during cooking or vacuum cleaning activities. The Commission of European Communities recommended a default value of 8% (Monchaux et al. 1999).

Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. The compartmental model represents particle deposition and time-dependent particle transport in the respiratory tract (see Figure 3-3) with reference values presented in Table 3-9. This table provides

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Table 3-9. Reference Values of Parameters for the Compartment Model to Represent Time-Dependent Particle Transport from the Human Respiratory Tract

Part A

| Clearance rates for insoluble particles | | | | |
|---|-------------------|------------------|-------------------------|------------------------|
| Pathway | From | To | Rate (d ⁻¹) | Half-life ^a |
| m _{1,4} | Al ₁ | bb ₁ | 0.02 | 35 days |
| m _{2,4} | Al ₂ | bb ₁ | 0.001 | 700 days |
| m _{3,4} | Al ₃ | bb ₁ | 1x10 ⁻⁴ | 7,000 days |
| m _{3,10} | Al ₃ | LN _{TH} | 2x10 ⁻⁵ | No data |
| m _{4,7} | bb ₁ | BB ₁ | 2 | 8 hours |
| m _{5,7} | bb ₂ | BB ₁ | 0.03 | 23 days |
| m _{6,10} | bb _{seq} | LN _{TH} | 0.01 | 70 days |
| m _{7,11} | BB ₁ | ET ₂ | 10 | 100 minutes |
| m _{8,11} | BB ₂ | ET ₂ | 0.03 | 23 days |
| m _{9,10} | BB _{seq} | LN _{TH} | 0.01 | 70 days |
| m _{11,15} | ET ₂ | GI tract | 100 | 10 minutes |
| m _{12,13} | ET _{seq} | LN _{ET} | 0.001 | 700 days |
| m _{14,16} | ET ₁ | Environment | 1 | 17 hours |

See next page for Part B

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Table 3-9. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

| Partition of deposit in each region between compartments ^b | | |
|---|-------------------|--|
| Region or deposition site | Compartment | Fraction of deposit in region assigned to compartment ^c |
| ET ₂ | ET ₂ | 0.9995 |
| | ET _{seq} | 0.0005 |
| BB | BB ₁ | 0.993-f _s |
| | BB ₂ | f _s |
| | BB _{seq} | 0.007 |
| bb | bb ₁ | 0.993-f _s |
| | bb ₂ | f _s |
| | bb _{seq} | 0.007 |
| Al | Al ₁ | 0.3 |
| | Al ₂ | 0.6 |
| | Al ₃ | 0.1 |

^aThe half-lives are approximate since the reference values are specified for the particle transport rates and are rounded in units of days⁻¹. A half-life is not given for the transport rate from Al₃ to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-life of compartment Al₃ is determined by the sum of the clearance rates.

^bSee paragraph 181, Chapter 5 (ICRP 1994b) for default values used for relating f_s to d_{ae}.

^cIt is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ae} \leq 2.5\sqrt{\rho/\chi} \mu\text{m} \text{ and}$$

$$f_s = 0.5e^{0.63(d_{ae}\sqrt{\rho/\chi}-2.5)} \text{ for } d_{ae} > 2.5\sqrt{\rho/\chi} \mu\text{m}$$

where

| | | |
|-----------------|---|---------------------------------------|
| f _s | = | fraction subject to slow clearance |
| d _{ae} | = | aerodynamic particle diameter/(μm) |
| ρ | = | particle density (g/cm ³) |
| χ | = | particle shape factor |

Al = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; ET = extrathoracic region; ET_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; GI = gastrointestinal; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994b

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clearance rates, expressed as a fraction per day and also as half-time (Part A), and deposition fractions (Part B) for each compartment for insoluble particles. ICRP (1994b) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution and, as particles dissolve, absorption rates tend to change over time. By creating a model with compartments of different clearance rates within each region (e.g., BB_1 , BB_2 , BB_{seq}), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles end up being swallowed. In the front part of the nasal passages (ET_1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs of a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles is cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as much as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly when it is closer to the alveoli. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB_2 and bb_2 , with both fractions having clearance half-times estimated at 20 days. Particle size is a primary determinant of the

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fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

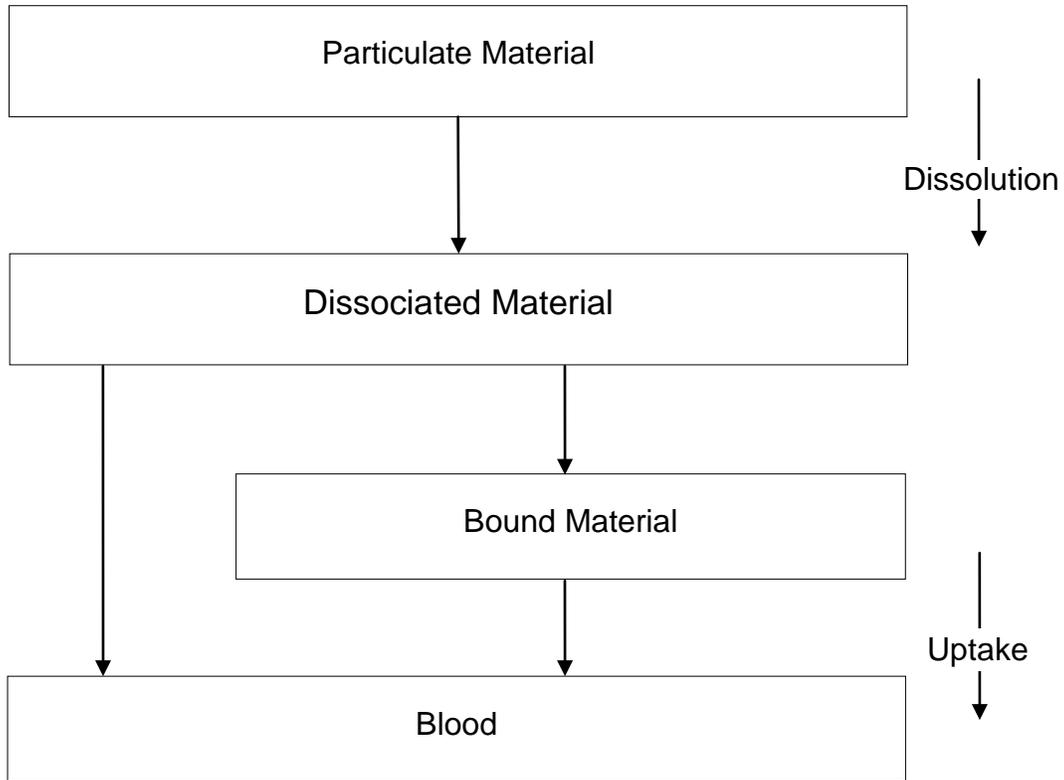
If particles reach and become deposited in the alveoli, they tend to become imbedded in the fluid on the alveolar surface or move into the lymph nodes. Coughing is the one mechanism by which particles are physically resuspended and removed from the AI region. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow.

In the alveolar-interstitial region, human lung clearance has been measured. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and the remaining 70% are assigned a half-time of several hundred days. Over time, AI particle transport falls, and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 3-5. First, there is a dissociation (dissolution) of particles; then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2 . Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET; for mouth breathing, the value is 50%.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2 . Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.
- For Type V, complete absorption (100%) is considered to occur instantaneously.

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Figure 3-5. The Human Respiratory Tract Model: Absorption into Blood

Source: ICRP 1994b

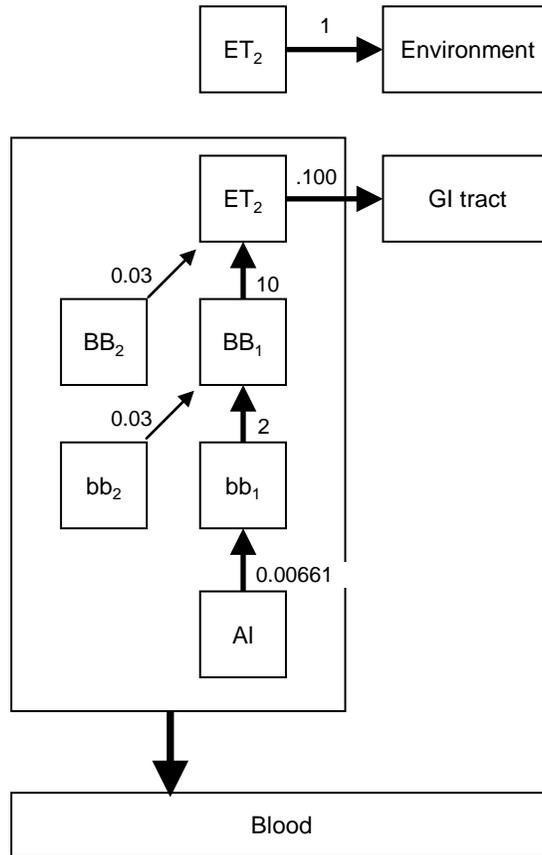
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ICRP (1994b) assigned gases and vapors to Type F, unless alternative values for absorption rates are available. However, alternatives to this assumption have been explored, including instantaneous partitioning of radon gas into dissolved blood (Butterweck et al. 2002). Radiation doses from exposures to radon have been estimated assuming radon and its progeny behave as Type F or Type M (Kendall and Smith 2002). The difference between the two categories is important for estimating tissue specific radiation dose coefficients (e.g., Sv/Bq inhaled) because of the relatively fast decay of radon ($t_{1/2}=3.8$ days) and its short-lived progeny (e.g., ^{218}Po , $t_{1/2}=3.05$ minutes; ^{214}Pb , $t_{1/2}=26.8$ minutes; ^{214}Bi , $t_{1/2}=19.7$ minutes). Type F materials (absorption $t_{1/2}=10$ minutes) will have a smaller proportion of progeny formed in the respiratory tract (i.e., prior to clearance) and, as a result, will deliver a smaller internal radiation dose and smaller dose to the respiratory tract relative to systemic tissues. Type M materials (absorption $t_{1/2}=100$ days for 90% of deposited material, $t_{1/2}=10$ minutes for 10%) will have a larger portion of progeny formed in the respiratory tract, which will deliver a larger internal radiation dose and larger dose to the respiratory tract relative to systemic tissues (Kendall and Smith 2002). Absorption $t_{1/2}$ values for ^{212}Pb and ^{212}Bi , in an aerosol having an activity median particle diameter of approximately 160 nm (range 50–500 nm), a value typical of attached radon progeny particles, were estimated to be approximately 10 and 13 hours, respectively (Marsh and Birchall 1999). Use of a $t_{1/2}$ value of 10 hours for radon progeny in the ICRP (1994b) model results in predicted radiation dose coefficients that are similar in magnitude to the Type M assumption (Kendall and Smith 2002). However, absorption of unattached radon progeny may be faster than that of attached particles. Absorption half-times for aerosols having approximately 0.3–3 nm in diameter, typical of unattached progeny particles, were estimated to be approximately 68 minutes (range 56–86) for ^{218}Po and ^{214}Pb and 18 minutes (range 17–21) for ^{214}Bi (Butterweck et al. 2002). Butterweck et al. (2002) proposed that binding of unattached radon progeny in the respiratory tract may result in slower absorption kinetics. They proposed that a 10-hour $t_{1/2}$ would apply to the unattached fraction after binding in the respiratory tract and that the unbound fraction may have an absorption $t_{1/2}<10$ minutes (see Section 3.4.1.1 for further discussion of absorption estimates).

The Radon Dose Evaluation Program (RADEP) implements a simplified version of the ICRP (1994b) model and is designed to simulate radon and radon progeny radiation dosimetry (Marsh and Birchall 2000; Figure 3-6): (1) the alveolar interstitial compartment is represented as a single compartment that has a particle transport rate of 0.00661 d^{-1} to the fast bronchiolar compartment, bb_1 ; (2) sequestered compartments, ET_{seq} , BB_{seq} , and bb_{seq} are not considered; (3) radon progeny are assumed to not bind to the respiratory tract; and (4) hygroscopic growth of unattached particles is simulated.

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Figure 3-6. Simplified Version of the Human Respiratory Tract Model (HRTM)



Source: Marsh and Birchall 2000

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Validation of the Model. ICRP (1994b) and RADEP have been evaluated with data on deposition and clearance of inhaled particulate aerosol and gases in humans and absorption of radon progeny (ICRP 1994b; Ishikawa et al. 2003b; Marsh and Birchall 1999). Sensitivity and uncertainty analyses of model predictions have been reported (Marsh and Birchall 2000; Yu et al. 2006).

Risk Assessment. The model has been used to establish the radiation dose (Sv) per unit of inhaled radon (Bq) for ages 3 months to 70 years (Kendall and Smith 2002).

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to specific inhalation exposures to radionuclides. Dose coefficients for radon and progeny have been estimated for all major organs, including the bone surfaces, bone marrow, and liver, and other tissues (Kendall and Smith 2002).

Species Extrapolation. The model is based on both human and animal data. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

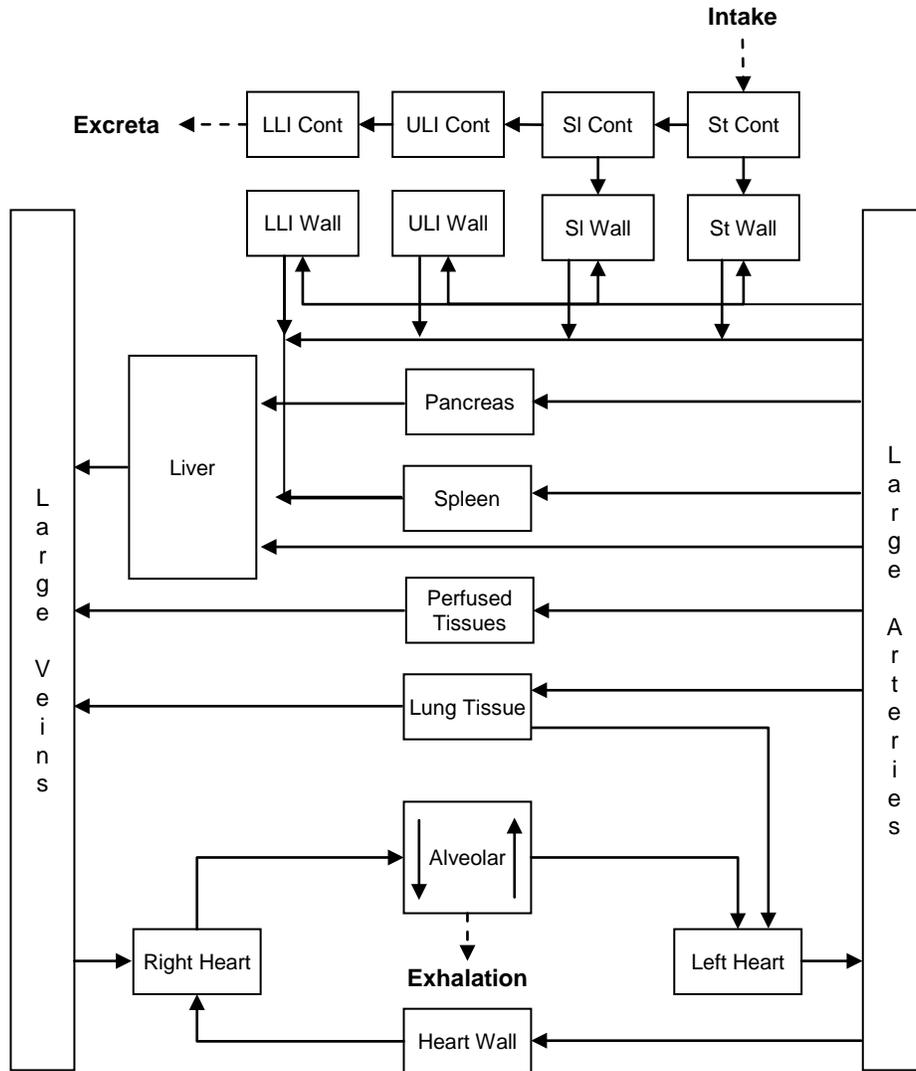
Interroute Extrapolation. The ICRP model is designed to simulate kinetics of inhaled radionuclides. (Note: ICRP/NCRP models are for normal lungs, not those of smokers.)

National Research Council Radon PBPK Model (NAS 1999b)

NAS (1999b) developed a PBPK model for simulating absorption and distribution of ingested or inhaled radioactive materials, including radon gas (Figure 3-7). NAS noted that statistically significant excesses of mortality from leukemia; esophagus, stomach, colon, liver, lung, breast, ovary, and urinary tract cancers; and multiple myeloma had been associated with atomic bomb survivors, but other epidemiological studies were used to establish risk models for thyroid and breast (based mainly on medical exposure data), bone (from radium exposures), and liver (from thoratrast) cancers, along with laboratory animal study data. The NAS cancer risk estimates were based on calculations with specific cancer site risk projection models using the computational method described in Federal Guidance Report No. 13 (EPA 1999a). The model simulates absorption of inhaled radon and distribution to tissues as flow-limited processes (i.e., tissue clearance equivalent to tissue blood flow) with parameters for tissue volumes, blood flow, and blood:tissue partition coefficients. Absorption of radon gas from the stomach and small intestine is simulated as diffusion-limited transfer from the lumen to the wall (i.e., vascularized

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Figure 3-7. Schematic Diagram of the NAS (1999b) PBPK Model Developed to Describe the Fate of Radon within Systemic Tissues



Source: NAS 1999b

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submucosa), and flow-limited exchange between blood and wall. A separate model is described in NAS (1999b) for estimating wall diffusion rate constants, which predicts a time-integrated radon concentration in the stomach wall of approximately 30% of that of the lumen. Parameter values for adults are presented in Table 3-10. Values for blood flows were derived from Leggett and Williams (1991, 1995); volumes and densities from ICRP (1990); and tissue:blood partition coefficients from Nussbaum and Hursh (1957). Parameter values for infants, children, and adolescents are also presented in NAS (1999b).

Validation of the Model. The NRC model has been evaluated with data on deposition and clearance of inhaled particulate aerosols and gases in humans and absorption of radon progeny (Correia et al. 1988; Crawford-Brown 1989; Harley and Robbins 1994; Harley et al. 1994; Hursh et al. 1965; NAS 1999b).

Risk Assessment. The model has been used to establish the radiation dose (Sv) per unit of inhaled or ingested radon (Bq) for ages 3 months to 70 years (NAS 1999b).

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to inhalation or ingestion exposures to radon. Dose coefficients for radon and progeny have been estimated for all major organs, including the bone surfaces, bone marrow, and liver, and other tissues (NAS 1999b).

Species Extrapolation. The model is based on both human and animal data. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

Interroute Extrapolation. The model is designed to simulate kinetics of inhaled or ingested radon. Extrapolation to other routes of external exposure would require modifications of the model to simulate absorption from those routes.

Khursheed (2000) Model

Khursheed (2000) developed a PBPK model for simulating absorption and distribution of ingested or inhaled radon gas (Figure 3-8). The model is similar in structure to the NRC (NAS 1999b) model, with the addition of a tissue compartment representing breast. The model has not had widespread use in risk assessment, relative to that of ICRP (1994b), RADEP, or the NRC (NAS 1999b) models. Absorption of inhaled and ingested radon, and distribution to tissues, are simulated as flow-limited processes (i.e., tissue clearance equivalent to tissue blood flow) with parameters for tissue volumes, blood flow, and

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Table 3-10. Parameters in the NAS (1999b) PBPK Model^a

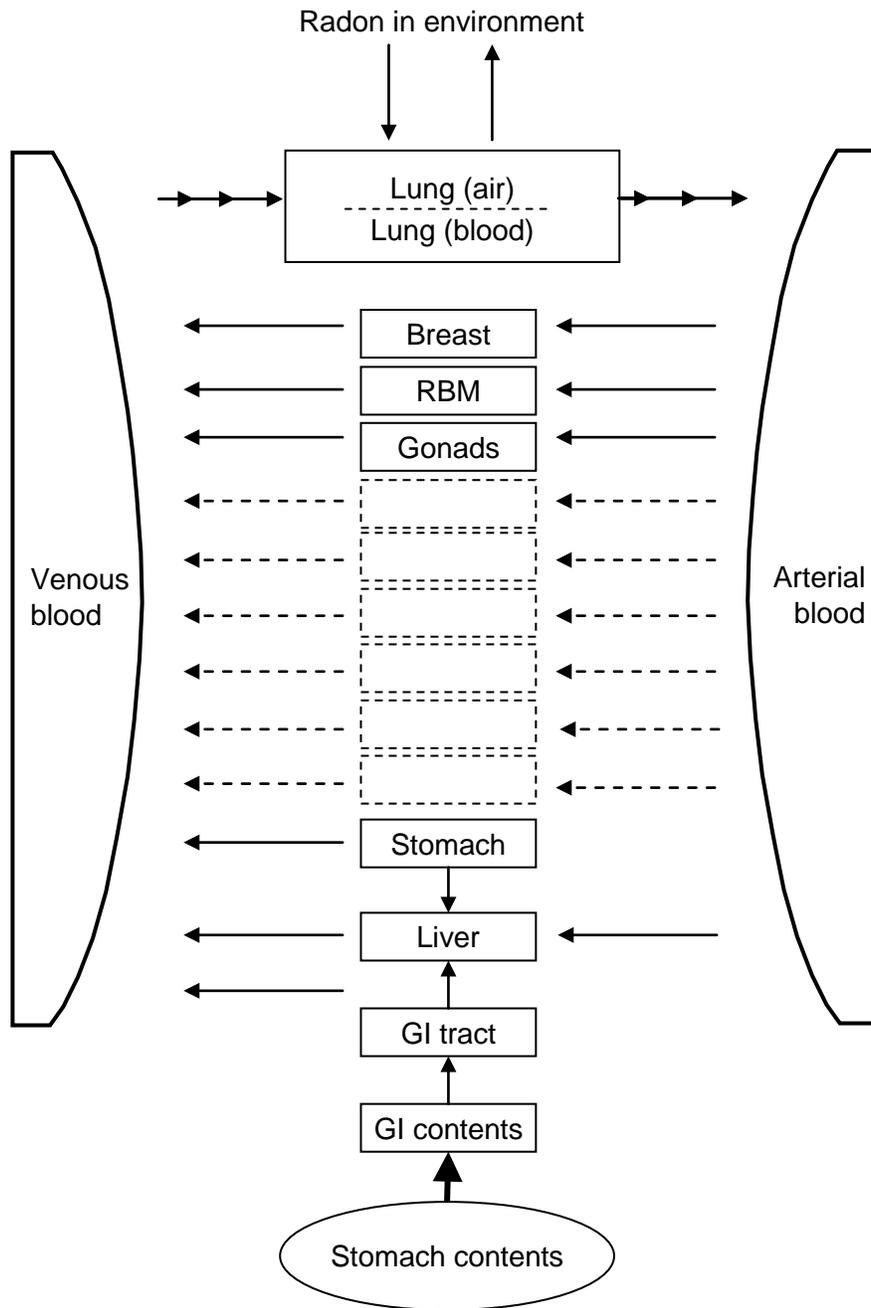
| Compartment | Flow (percent cardiac output) | Tissue mass (kg) | Tissue density | Tissue:blood partition coefficient |
|----------------------------|-------------------------------|------------------|----------------|------------------------------------|
| Stomach wall | 1.0 | 0.15 | 1.05 | 0.7 |
| Small intestine wall | 10.0 | 0.64 | 1.04 | 0.7 |
| Upper large intestine wall | 2.0 | 0.21 | 1.04 | 0.7 |
| Lower large intestine wall | 2.0 | 0.16 | 1.04 | 0.7 |
| Pancreas | 1.0 | 0.10 | 1.05 | 0.4 |
| Spleen | 3.0 | 0.18 | 1.05 | 0.7 |
| Adrenals | 0.3 | 0.014 | 1.02 | 0.7 |
| Brain | 12.0 | 1.4 | 1.03 | 0.7 |
| Heart wall | 4.0 | 0.33 | 1.03 | 0.5 |
| Liver | 6.5 | 1.8 | 1.04 | 0.7 |
| Lung tissue | 2.5 | 0.47 | 1.05 | 0.7 |
| Kidneys | 19.0 | 0.31 | 1.05 | 0.66 |
| Muscle | 17.0 | 28.0 | 1.04 | 0.36 |
| Red marrow | 3.0 | 1.5 | 1.03 | 8.2 |
| Yellow marrow | 3.0 | 1.5 | 0.98 | 8.2 |
| Trabecular bone | 0.9 | 1.0 | 1.92 | 0.36 |
| Cortical bone | 0.6 | 4.0 | 1.99 | 0.36 |
| Adipose tissue | 5.0 | 12.5 | 0.92 | 11.2 |
| Skin | 5.0 | 2.6 | 1.05 | 0.36 |
| Thyroid | 1.5 | 0.02 | 1.05 | 0.7 |
| Testes | 0.05 | 0.035 | 1.04 | 0.43 |
| Other | 3.2 | 3.2 | 1.04 | 0.7 |

^aValues shown for physiological parameters (flows, masses, densities) are for adults.

Source: NAS 1999b

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Figure 3-8. Khursheed (2000) PBPK Model for Inhalation and Ingestion of Radon Gas



Source: Khursheed 2000

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blood:tissue partition coefficients (Table 3-11). Values for blood flows were derived from Leggett and Williams (1991, 1995); and tissue volumes were derived from ICRP (1990). Tissue:blood partition coefficients were derived from Nussbaum and Hursh (1957); however, a single value (0.36) was adopted for all soft tissues, with a higher value used for the gastrointestinal tract and stomach to account for higher fat content of these tissues. Values for partition coefficients for breast and red marrow assumed 30 and 40% fat content, respectively. Although age-dependence of radon biokinetics is discussed in Khursheed (2000), age-specific parameter values for the model are not reported.

Validation of the Model. The model has been evaluated with data on whole body retention kinetics of radon following ingestion of radon in water (Hursh et al. 1965; Khursheed 2000).

Risk Assessment. The model has been used to predict tissue-specific annual radiation doses associated with continuous inhalation exposures to 20 Bq/m³ of radon, or following ingestion of 1 Bq of radon (Khursheed 2000).

Target Tissues. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to inhalation or ingestion exposures to radon. Dose coefficients for radon and progeny have been estimated for major organs, including the bone surfaces, bone marrow, and liver, and other tissues (Khursheed 2000).

Species Extrapolation. The model is based on both human and animal data (e.g., partition coefficients). However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

Interroute Extrapolation. The model is designed to simulate kinetics of inhaled or ingested radon. Extrapolation to other routes of external exposure would require modifications of the model to simulate absorption from those routes.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in Section 3.4 (Toxicokinetics), the radionuclide radon-222 (²²²Rn; radioactive half-life of 3.82 days) is an inert noble gas found in air and some deep well water sources. Radon occurs in air and water along with its short-lived radioactive progeny (i.e., ²¹⁴Bi, ²¹⁴Pb, ²¹⁸Po). Deposition and absorption

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Table 3-11. Parameters in Khursheed (2000) PBPK Model for Radon Gas

| Tissue | Tissue:blood partition coefficient | Tissue blood flow (L/minute) | Tissue volume (L) |
|-------------------------------------|------------------------------------|------------------------------|-------------------|
| Lung (blood) | | 6.5 | 0.52 |
| Lung (air) | 2.33 | | 2.82 |
| Breast | 3.07 | 0.015 | 0.35 |
| Red bone marrow | 4.70 | 0.195 | 1.46 |
| Gonads | 0.360 | 0.00325 | 0.033 |
| Brain | 0.411 | 0.78 | 1.25 |
| Kidneys | 0.33 | 1.23 | 0.295 |
| Muscle | 0.36 | 1.11 | 26.5 |
| Other | 0.36 | 1.05 | 25.1 |
| Adipose | 11.2 | 0.325 | 16.4 |
| Bone | 0.21 | 0.13 | 2.27 |
| Liver | 0.36 | 1.66 | 1.7 |
| Gastrointestinal (upper intestines) | 0.411 | 1.17 | 0.95 |
| Stomach wall | 0.411 | 0.065 | 0.14 |
| Arterial blood | | 6.5 | 0.556 |
| Venous blood | | 6.5 | 1.19 |

Source: Khursheed 2000

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of inhaled or ingested radon gas will be determined largely by its solubility in tissues and blood flow to the lungs or gastrointestinal tract (i.e., absorption rate will be flow-limited). Distribution of radon and its clearance from the blood following exposure will be governed by its solubility in water and fat and blood flow rates to major tissue depots for radon (i.e., fatty tissues). Absorbed radon is quickly eliminated from the blood by diffusion across the lung, followed by exhalation. Radon can be absorbed through the skin, as demonstrated by its appearance in the blood following dermal exposure; however, underlying mechanisms have not been elucidated.

The pharmacokinetics of inhaled radon progeny will be determined by physiological and physico-chemical characteristics (i.e., relative proportions of particular radon progeny and particle size (unattached particles with diameters of 0.5–3 nm to attached particles with diameters of 50–1,500 nm). The relative proportions vary with exposure conditions (i.e., indoor, outdoor), activities of the individual (e.g., sleeping, activities that release particulates into the air), smoking, and other aerosol-generating activities (i.e., vacuum cleaning, cooking, fireplace and circulating fan usage). Amounts and location of deposition of radon progeny will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. Absorption of ingested radon progeny, and progeny formed from radon after ingestion, will be influenced by rates of transfer of stomach contents into the small intestine, as well as rates of absorption of progeny from the small intestine. Specific mechanisms involved in absorption of radon progeny from the small intestine have not been completely elucidated; however, based on our understanding of lead absorption, it is likely that the mechanisms include those common to other divalent cations (e.g., membrane cation transporters and channels). Information regarding the distribution and elimination of radon progeny (bismuth, lead, and polonium) can be found in reviews of these subjects (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 1995c). The largest fractions of the body burdens for radon progeny would be expected to be found in bone for lead, kidney for bismuth, and liver for polonium (Agency for Toxic Substances and Disease Registry 2007b; ICRP 1980, 1994c, 2001).

3.5.2 Mechanisms of Toxicity

Extensive efforts have been made to elucidate mechanisms responsible for ionizing radiation-induced adverse effects. The Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999b) includes an in-depth discussion of mechanisms of biological effects of ionizing radiation in general. Summaries of available information regarding underlying mechanisms of radon-induced lung cancer include Evans (1991, 1992) and, more recently, Jostes (1996) and NAS (1999a,

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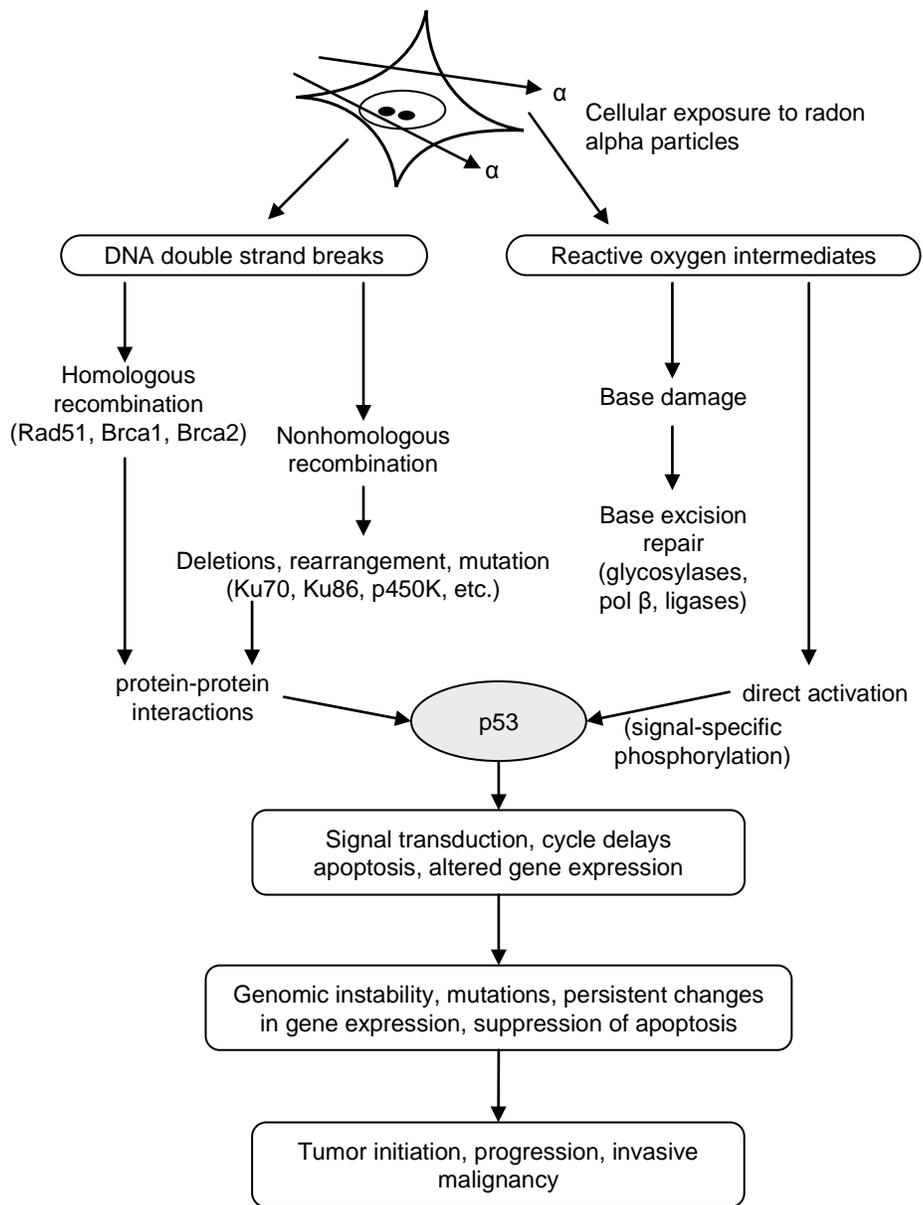
1999b). The intent of this Toxicological Profile for Radon is to provide a brief overview of the present state of the science regarding mechanisms that may play roles in radon-induced lung cancer. The information in this section is summarized predominantly from Chapter 6 (Molecular and Cellular Mechanisms of Radon-Induced Carcinogenesis) of the Risk Assessment of Radon in Drinking Water produced for the National Academy of Sciences (NAS 1999b). The reader is referred to this source for more detailed information on mechanisms of radon-induced lung cancer.

Toxicity of radon derives primarily from the biological effects of alpha radiation released during the radiological decay of radon progeny, particularly ^{218}Po and ^{214}Bi (attributed to essentially instantaneous decay of ^{214}Po to ^{210}Pb following its formation via beta and gamma decay of ^{214}Bi). The sequence of events leading from irradiation of living cells involves ionization that causes cellular damage that includes DNA breakage, accurate or inaccurate repair, apoptosis, gene mutations, chromosomal change, and genetic instability (Kronenberg 1994; Ward 1988, 1990). Figure 3-9 depicts a general conceptual model of the biology leading from alpha irradiation of cells by radon and radon progeny to tumor development (NAS 1999b). The process includes a series of events by which radiation-induced molecular changes affect the normal functions of regulatory genes, leading to genomic instability, loss of normal cell and tissue homeostasis, and development of malignancy.

One pathway leading to tumor formation begins with the induction of DNA damage to irradiated cells (Figure 3-9). The average track of alpha particles through a spherical cell nucleus can cross many individual strands of DNA, depositing energy in ion clusters and producing corresponding numbers of double-strand breaks, known as multiply locally damaged sites (MLDSs) (Ward 1990). Double-strand breaks are the most prominent form of DNA damage to cells irradiated by radon alpha particles. Such double-strand breaks can be repaired by homologous or nonhomologous (illegitimate) rejoining. In homologous repair, pairing proteins such as rad51 and associated modulatory proteins, pair a DNA terminus with the intact DNA homolog. A major signaling protein (p53) that regulates cell-cycle control, apoptosis, and the transcription of many downstream genes may interact with rad51 and suppress rad51-dependent DNA pairing. However, homologous repair of DNA is likely to be highly accurate because sequence information from the intact chromatid is used to repair the broken DNA. The nonhomologous recombination pathway involves end-to-end rejoining of broken DNA ends by supporting proteins including Ku70, Ku86, p450 kinase, and DNA ligase IV. The end result of DNA breakage and rejoining via this pathway may include some degree of deletion, insertion, or rearrangement of genetic material, which can persist over many cell generations.

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Figure 3-9. Conceptual Model of the Biology Leading From Alpha Irradiation of Cells by Radon and Radon Progeny to Tumor Development



Source: NAS 1999b

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Ionizing radiation that does not directly damage DNA can produce reactive oxygen intermediates that directly affect the stability of p53, resulting in downstream effects on cell regulation and activate cellular systems sensitive to the cellular redox states. Reactive oxygen intermediates can also produce oxidative damage to individual bases in DNA and point mutations by mispairing during DNA replication. Such damage can be repaired by the base-excision repair system which involves glycosylases, polymerase β , and ligases.

The p53 protein plays a critical role in regulating responses that are elicited in damaged cells, particularly responses involving cell-cycle arrest and apoptosis. The p53 protein also interacts with other regulatory and repair proteins. In the presence of cellular damage via direct DNA damage or via reactive oxygen intermediates, the lifetime of p53 increases, which can result in cell cycle delays and apoptosis. Surviving cells may contain gene deletions, rearrangements, amplifications, and persistent genomic instability. Resultant mutations in oncogenes, loss of function in tumor suppressors, and loss of heterozygosity can lead to tumor initiation, progression, and invasive malignancy.

The cells most likely involved in a carcinogenic response to ionizing radiation such as alpha irradiation of the lung by inhaled radon and radon progeny are the cells that incur genetic damage or altered genomic stability, not cells that receive lethal damage. At relatively low exposure levels, most irradiated cells would be expected to survive. The strong synergism between radon exposure and cigarette smoking may be the result of initial radon exposure that produces damaged, yet viable, cells that are further affected by carcinogens in cigarette smoke (Brenner and Ward 1992; Moolgavkar et al. 1993).

Both tobacco smoke and ionizing radiation are known to induce oxidative stress via reactive oxygen species (ROS). Under the assumption that glutathione-S-transferase M1 (*GSTM1*) null homozygotes would exhibit decreased ability to neutralize ROS, Bonner et al. (2006) used a case-only design to assess the *GSTM1* genotype of lung cancer cases for whom long-term α -track radon detectors had been used to measure residential radon concentrations. Second-hand smoke levels were also estimated. Radon concentrations in excess of 121 Bq/m³ (3.27 pCi/L) were significantly associated with *GSTM1* null homozygotes compared to *GSTM1* carriers; an odds ratio for second-hand smoke and *GSTM1* interaction among never smokers was elevated as well. The results provide suggestive evidence that radon and second-hand smoke might promote carcinogenic responses via a common pathway.

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A recent study reported a lack of expression of the p16Ink4a protein (Ink4a is a tumor suppressor gene) in 50% of radon-induced lung tumors of rats, suggesting that deregulation of p16Ink4a may play a role in lung tumors induced by radon and radon progeny (Bastide et al. 2009).

3.5.3 Animal-to-Human Extrapolations

Epidemiological studies clearly identify lung cancer as the health effect of greatest concern, both from occupational and residential exposure to radon and its progeny. Results of studies assessing the health effects of exposure to radon in a variety of animal species indicate that rats and dogs are relatively sensitive to radon-induced lung tumor development, whereas hamsters and mice did not develop tumors, even at cumulative exposures >10,000 WLM. This species difference may represent a real difference in sensitivity to radon; however, other factors may also have contributed to the lack of tumors in mice and hamsters, including decreased longevity in some exposed groups (i.e., animals die before tumors could develop) and termination of exposure or observations prior to the development of lung tumors. The lack of demonstrated exposure-related lung cancer in the hamsters may reflect species-specific resistance to alpha radiation-induced lung tumors since similar negative results were observed in hamsters exposed to plutonium, another alpha-emitting radionuclide (Sanders 1977). Based on a wide range of species differences in susceptibility to radon-induced lung cancer and insufficient information regarding mechanisms of interspecies differences in susceptibility, animal-to-human extrapolations for purposes of risk assessment do not appear useful at this time, nor are they needed given the wealth of epidemiological data.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to

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convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Radon itself is a noble gas and would not have hormonally active properties. In addition, no studies were located regarding endocrine disruption in humans and/or animals after exposure radon progeny.

No *in vitro* studies were located regarding endocrine disruption associated with radon progeny.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous substances. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

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Children sometimes differ from adults in their susceptibility to hazardous substances, but whether there is a difference depends on the substance (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from substance insults. Children also have a longer remaining lifetime in which to express damage from substances; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same substance. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Available information from children employed as miners in China does not provide evidence of increased susceptibility to the effects of exposure to radon (Lubin et al. 1990; NIH 1994). However, a child in a smoking household will receive a higher radiation dose from radon (and is therefore more susceptible) than one in a nonsmoking household based on exposures to the same concentration of radon because cigarette smoke increases the attached fraction (HPA 2009), which in turn increases the radiation dose. Age-related differences in susceptibility to the effects of exposure to radon and radon progeny have not been demonstrated. Differences in lung morphometry and breathing rates in children could result in higher estimated radiation doses relative to adults (NCRP 1984a; Samet et al. 1989).

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3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Normally, a biomarker of exposure is defined as a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). This does not apply to radon or its progeny since they are naturally present in individuals, and xenobiotics are not. The preferred biomarkers of exposure to radon and radon progeny are the substances themselves in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), radon and all of its progeny may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to radon and radon progeny are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by radon and radon progeny are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11, Populations That Are Unusually Susceptible.

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3.8.1 Biomarkers Used to Identify or Quantify Exposure to Radon and Radon Progeny

Biomarkers of exposure to radon and its progeny include the presence of radon progeny in several human tissues and fluids, including bone, teeth, blood, hair, and whiskers; these progeny can be quantified by methods which are both specific and reliable (Blanchard et al. 1969; Clemente et al. 1984; Gotchy and Schiager 1969). Although the presence of radon progeny in these tissues and fluids indicates exposure to radon and radon progeny, particularly as a consequence of absorption of inhaled radon and radon progeny and ingestion of food or water containing radon-producing radionuclides such as uranium and thorium, exposure to uranium or radium may also result in the presence of these decay products. The isotope ^{210}Po may also be found in tissues after exposure to cigarette smoke. Levels of ^{210}Pb in teeth have been associated with levels of radon in the environment in an area with high natural background levels of radon and its progeny (Clemente et al. 1984). Black et al. (1968) reported a correlation between radiation exposure and ^{210}Pb levels in bone from uranium miners. However, cumulative exposure to these individuals was estimated. Biomarkers of exposure to radon or its progeny may be present after any exposure duration (e.g., acute, intermediate, chronic). Because of the relatively short half-lives of most radon progeny, with respect to a human lifetime, the time at which the biological sample is taken related to time of exposure may be important. However, for the longer-lived progeny the time factor is less critical.

Models are available which estimate exposure to radon and its progeny, ^{210}Pb and ^{210}Po , in bone, teeth, and blood (Blanchard et al. 1969; Clemente et al. 1982, 1984; Eisenbud et al. 1969; Gotchy and Schiager 1969; Weissbuch et al. 1980). However, these models make numerous assumptions, and uncertainties inherent in all models are involved in these estimates. Therefore, at present, these estimated levels of biomarkers of exposure are not useful for quantifying exposure to radon and its progeny.

3.8.2 Biomarkers Used to Characterize Effects Caused by Radon and Radon Progeny

The principal target organ identified in both human and animal studies following exposure to radon and its progeny is the lung. Alterations in sputum cytology have been evaluated as an early indicator of radiation damage to lung tissue. The frequency of abnormalities in sputum cytology, which may indicate potential lung cancer development, increased with increasing cumulative exposures to radon and its progeny (Band et al. 1980; Saccomanno et al. 1974). Abnormal sputum cytology can be used in diagnosis of lung cancer (Rivera et al. 2003). Abnormal sputum cytology may be observed following radon exposure, as well as exposure to other carcinogens such as cigarette smoke; it is not recommended as a screening tool for radon exposure. In addition, even though increases in the frequency of abnormal

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sputum cytology parameters can be measured, they may not provide reliable information regarding predicted health effects in exposed individuals.

Associations between chromosomal aberrations and environmental levels of radon have been reported (Pohl-Rüling and Fischer 1983; Pohl-Rüling et al. 1976, 1987). Signs of genotoxicity in underground miners exposed to radon and other potentially genotoxic substances include increased frequencies of chromosomal aberrations and micronuclei in lymphocytes (Bilban and Jakopin 2005; Broman et al. 1978; Smerhovský et al. 2001, 2002) and increased frequency of mutations of glycophorin A in blood (Shanahan et al. 1996). However, these genotoxic effects cannot be exclusively attributed to exposure to radon and its progeny.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Interactions of radon, cigarette smoke, arsenic, crystalline silica dust, and diesel exhaust particulates and the possible effects on radon-induced toxicity is an actively-researched complex issue. Cigarette smoke appears to interact with radon and its progeny to potentiate their effects. In general, epidemiological studies have reported synergistic, multiplicative, or additive effects of cigarette smoke in lung cancer induction among miners exposed to radon and its progeny (see NAS 1999a for an in-depth discussion of interactions between smoking and exposure to radon).

Some studies of occupational exposure to radon and radon progeny provide information to indicate that lung cancer was more prevalent among exposed workers who smoked compared to nonsmoking workers. For example, studies by Lundin et al. (1969, 1971) reported 10 times more lung cancer among U.S. uranium miners who smoked. Modeling results of Thomas et al. (1994), using data on lung cancer mortality in a Colorado Plateau uranium mining cohort, indicated a multiplicative synergistic relationship between lung cancer mortality and exposure to radon among smokers. Modeling results of data from another mining cohort in China (Yao et al. 1994) suggested that the synergistic effect of radon exposure and smoking was greater than additive and less than multiplicative; furthermore, the risk of lung cancer was higher if smoking and exposure to radon progeny occurred together rather than if smoking was initiated following the cessation of occupational exposure to radon progeny. Leuraud et al. (2011) assessed the effects of exposure to radon and radon decay products and smoking status on the risk of lung cancer in a combined analysis of 1,046 lung cancer cases and 2,492 controls with detailed radon exposure data and smoking status selected from three major miner cohorts in the Czech Republic (Tomášek et al. 2003), France (Laurier et al. 2004), and Germany (Kreuzer et al. 2010). The combined analysis resulted

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in a significant excess risk of lung cancer with and without adjustment for smoking; the study authors indicated that the results of the combined analysis suggest a sub-multiplicative interaction between radon exposure and smoking. Analysis of pooled results from 13 European residential case-control studies resulted in findings that the absolute risk of death from lung cancer at age 75 years at usual residential radon concentrations of 0, 100, and 400 Bq/m³ (0, 2.7, and 10.8 pCi/L) would be 25 times greater for cigarette smokers than lifelong nonsmokers (Darby et al. 2005, 2006). It should be noted that these studies were typically limited by lack of adjustment for concomitant exposure to other known or probable human carcinogens such as arsenic, crystalline silica dust, and diesel exhaust particulates.

Interactions between radon and arsenic were evaluated in a cohort of Chinese tin miners (Xuan et al. 1993). A 75% reduction in the lung cancer risk was indicated after adjusting for arsenic exposure. In another study (Bergdahl et al. 2010), decreased lung cancer risk from radon exposure was indicated after adjusting for silica exposure within the highest exposure group of a cohort of Swedish iron ore miners. In a multistate study of 12,315 non-metal underground and surface workers exposed to diesel exhaust particulates at facilities in Missouri, New Mexico, Ohio, and Wyoming (Attfield et al. 2012), an SMR of 1.26 (95% CI 1.09–1.44) was calculated for mortality from lung cancer among the workers compared to state-based mortality rates.

Some animal studies support the theory that cigarette smoke potentiates the effects of radon and its progeny alone or in conjunction with uranium ore dust. A study by Chameaud et al. (1982b) reported an increase in the incidence of lung cancer, as well as a decrease in the cancer latency period in rats exposed to radon and then to cigarette smoke, compared to rats exposed to radon and its progeny alone. This study did not include untreated controls. Alterations in normal blood parameters, including carboxyhemoglobin levels and leukocyte counts, were observed in dogs exposed to cigarette smoke followed by exposure to radon progeny plus uranium ore dust, compared to animals exposed to only radon progeny plus uranium ore (Filipy et al. 1974). In contrast, some studies suggest an antagonistic interaction between smoking and radon progeny-induced lung cancer. Dogs exposed daily to cigarette smoke followed immediately by exposure to radon and its progeny and uranium ore dust exhibited a decrease in the incidence of lung tumors, compared to dogs exposed to radon and its progeny plus uranium ore dust (Cross et al. 1982b). Cross (1988) reported that this was possibly due to a thickening of the mucus layer as a result of smoking and, to a lesser extent, a stimulatory effect of cigarette smoke on mucociliary clearance, although no empirical evidence was collected during the experiment to test these possibilities.

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In rats, administration of chemicals present in cigarette smoke after exposure to radon and its progeny resulted in a decrease in the lung cancer latency period when compared to the time-to-tumor induction in animals treated with radon alone. This effect was seen with 5,6-benzoflavon (Queval et al. 1979) and cerium hydroxide (Chameaud et al. 1974).

Other airborne irritants, as well as ore dust and diesel exhaust, may act synergistically with radon and its progeny to increase the incidence of adverse health effects. Epidemiological and other studies report the presence of other airborne irritants in mining environments, including arsenic, hexavalent chromium, nickel, cobalt (Ševc et al. 1984), serpentine (Radford and Renard 1984), silica dust (Maciejewska 2008), iron ore dust (Damber and Larsson 1982; Edling and Axelson 1983; Radford and Renard 1984), and diesel exhaust (Damber and Larsson 1982; Ševc et al. 1984).

Cross and colleagues at Pacific Northwest Laboratory have conducted extensive experiments involving exposure of dogs, mice, rats, and hamsters to radon and its progeny in conjunction with uranium ore dust and/or diesel exhaust (Cross 1988; Cross et al. 1981a, 1982b, 1984; NIEHS 1978; Palmer et al. 1973). Studies in hamsters, mice, and rats have shown that exposure to uranium ore dust and/or diesel exhaust increases the pulmonary effects of radon. Radon and combinations of uranium ore dust and/or diesel exhaust produced greater incidences of pulmonary emphysema and fibrosis in hamsters than radon and its progeny alone (Cross 1988). Exposure to uranium ore dust or diesel exhaust alone caused significant bronchial hyperplasia, but not as great an effect as combining either of these with radon and its progeny. The incidence of severe lesions of the upper respiratory tract (nasal passages and trachea) of mice and rats was increased following exposure to radon and uranium ore dust, compared to animals exposed to radon and its progeny alone (Palmer et al. 1973). An increased incidence of thoracic cancer (40%) was observed in rats treated with asbestos (mineral dust) after inhalation of radon and its progeny, compared with animals exposed to radon alone (Bignon et al. 1983). However, these tumors may have been due to asbestos rather than to an interaction between agents. This experiment did not include a group exposed only to mineral dusts. In a study of tin miners in China, radon was found to account for only around 25% of the age-adjusted ERR/WLM once arsenic was accounted for as a confounder (Xuan et al. 1993). Inhalation exposure to radon and its progeny in conjunction with silicon dioxide increased the incidence of nodular fibrosis of the lungs in rats (Kushneva 1959).

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3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to a substance than will most persons exposed to the same level in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke), arsenic, crystalline silica dust, or diesel exhaust particulates. These parameters result in reduced detoxification or excretion of the substance, or compromised function of organs affected by the substance. Populations who are at greater risk due to their unusually high exposure are discussed in Section 6.7, Populations with Potentially High Exposures.

Smokers who are exposed to elevated levels of radon and radon progeny are at much higher risk of lung cancer than nonsmokers (Darby et al. 2005, 2006). Nonsmoking children in smoking households are more susceptible than nonsmoking children in nonsmoking households since smoke increases the attached fraction and therefore the radiation dose (HPA 2009). People who have chronic respiratory disease, such as asthma, emphysema, or fibrosis often have reduced expiration efficiency and increased residual volume (i.e., greater than normal amounts of air left in the lungs after normal expiration) (Guyton 1977). Radon progeny can remain in the lungs for long periods of time, increasing the risk of damage to the lung tissue. Persons who have existing lung lesions may be more susceptible to the tumor-causing effects of radon progeny (Morken 1973). In an assessment of lung cancer cases pooled from three residential case-control studies, radon concentrations $>121 \text{ Bq/m}^3$ (3.3 pCi/L) were associated with more than a 3-fold interaction odds ratio among glutathione-S-transferase M1 (GSTM1) null homozygotes compared to GSTM1 carriers (Bonner et al. 2006). In the study, it was hypothesized that GSTM1 null homozygotes would have decreased ability to neutralize reactive oxygen species induced by ionizing radiation and tobacco smoke. Thus, GSTM1 null homozygotes may exhibit increased susceptibility to the respiratory effects of radon progeny.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

As discussed in detail in Section 3.2.1 (Inhalation Exposure), lung cancer is the primary toxicity concern following long-term exposure to radon and radon progeny. The high-energy alpha emissions from radon progeny deposited in the airways are the source of toxicity concern. The sequence of events leading from irradiation of living cells is generally believed to involve ionization that causes cellular damage including DNA breakage, accurate or inaccurate repair, apoptosis, gene mutations, chromosomal change, and genetic instability. Cigarette smoke appears to interact with radon and its progeny to potentiate their effects.

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There are no known methods for reducing the toxic effects of radon once exposure has occurred. Inhaled radon, as a noble gas, is rapidly absorbed from the lung and readily excreted in exhaled air. Inhaled radon progeny that are attached to dust particles and tobacco products may lodge in the lung. Most radon progeny decay via alpha or beta emission with half-lives so short that conventional methods for reducing toxicity would be ineffective. Although selected radon progeny (e.g., ^{210}Po) have longer half-lives, conventional medical interventions such as pulmonary lavage carry significant risk and are not recommended. Methods for reducing the potential exposure to radon (and therefore its toxic effects) consist of periodically testing for radon in indoor air and reducing radon concentrations to below the EPA recommended action level of 4 pCi/L, using active soil depressurization (ASD) in existing homes and radon-reducing features in new home construction. If ASD does not reduce levels sufficiently, reversing the fan direction to pressurize the subslab can be used to determine the more effective method (Kearney and Mason 2011). Measures to prevent high radon levels in new home construction are expected to be effective at reducing radon-related lung cancer deaths, while remediating old homes with high radon levels may be more expensive and less effective. An additional method to reduce toxic effects of radon is to stop smoking (EPA 2009a; Mendez et al. 1998, 2011) since the presence of smoke particles increases the radiation dose from radon progeny. Point-of-entry mitigation methods for reducing radon levels in drinking water are recommended over mitigation at the tap since the latter is not effective for radon (EPA 2009a; 2012a).

3.11.1 Reducing Peak Absorption Following Exposure

There are no methods for reducing peak absorption of radon gas following exposure and radon progeny decay via alpha or beta emission so rapidly that efforts to remove inhaled radon progeny would be ineffective.

3.11.2 Reducing Body Burden

There are no known methods for reducing the body burden of absorbed radon and radon progeny.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There is an increasing amount of information regarding the possible efficacy of dietary micronutrients at reducing lung cancer risk in smokers. Alavanja (2002) published a review of tobacco smoke- and radon-induced damage and potential preventive interventions. Since smoking multiplies the risk of lung cancer

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from radon exposure, stopping smoking could significantly reduce the risk of radon induced lung cancer; however, reducing exposure to radon is a first consideration. It was noted that available data indicate that micronutrients associated with a reduction in lung cancer risk among smokers might also reduce the risk in nonsmokers, possibly via antioxidant properties. Thus, diets high in fruits and vegetables might be of benefit in neutralizing reactive oxygen species produced by cigarette smoke and radon. However, the American College of Chest Physicians does not recommend the use of supplements for the prevention of lung cancer as they have not been shown to be helpful, and beta-carotene has been associated with increases in lung cancer (Alberts 2007).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of radon is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of radon.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Radon

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to radon are summarized in Figure 3-10. The purpose of this figure is to illustrate the existing information concerning the health effects of radon. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments.

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Figure 3-10. Existing Information on Health Effects of Radon

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | ● | | | ● | | | ● | | ● | ● |
| Oral | | | | | | | | | | ● |
| Dermal | | | | | | | | | | |
| External | | | | | | | | | | |

Human

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | ● | ● | ● | ● | | | | | ● | ● |
| Oral | | | | | | | | | | |
| Dermal | | | | | | | | | | |
| External | | | | | | | | | | |

Animal

● Existing Studies

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Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-10 graphically describes whether a particular health effect end point has been studied for a specific route and duration of exposure. Most of the information on health effects in humans caused by exposure to radon and radon progeny was obtained from epidemiological studies of uranium and other hard rock miners. These studies of chronic occupational exposure to radon via inhalation provide information on cancer and lethality, and limited insight into reproductive and genetic effects. Limited information is also available regarding cancer following dermal exposure to radon and its progeny. No information on the health effects of radon and its progeny in humans was available following acute or intermediate exposure by any route. No information on the health effects of radon and its progeny in animals following acute, intermediate, or chronic oral or dermal exposure was located. The only information available from animal studies was by the inhalation route of exposure, which provides data on systemic and genetic effects, as well as cancer.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No data were located regarding adverse health effects in humans following acute exposure to radon and its progeny by any route. Single dose studies are available for laboratory animals that have been exposed by the inhalation and parenteral routes. No information is available on acute oral exposure in laboratory animals. Information is available on lethality following acute inhalation exposure to high doses. However, this study did not provide information on target organs, sensitive tissues, or cause of death. No information is available on effects in humans or animals following relatively low-level acute exposure to radon and its progeny. However, the greatest health concern for radon and its progeny is lung cancer, which results from long-term exposure, not acute-duration exposure. Studies designed to assess the potential for adverse health effects in humans following acute-duration exposure to radon and its progeny do not appear necessary at this time.

Intermediate-Duration Exposure. No data were located regarding adverse health effects associated with intermediate-duration exposure of humans to radon and its progeny by any exposure route. Epidemiological miner-based studies, in general, have focused on cohorts exposed to radon and its progeny for durations >1 year. Animal studies demonstrate that intermediate exposure to high levels of radon and its progeny can cause chronic respiratory toxicity and lung cancers and indicate that similar effects might occur following intermediate-duration exposure in humans. The relationship between the

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nature and severity of the respiratory toxicity and the amount of radon exposure is not clearly defined; nor is there any information regarding systemic toxicity following intermediate-duration exposure.

Additional research on the dose-duration-response relationship between radon exposure and the type and permanence of resulting toxicity would provide pertinent information. If populations exposed to radon and its progeny for intermediate durations can be identified, such populations could be assessed for potential adverse health outcomes.

Chronic-Duration Exposure and Cancer. Knowledge of the adverse health effects in occupationally-exposed humans following chronic-duration exposure to radon and its progeny is historically based on studies in adult male underground miners. These studies describe predominantly respiratory end points, such as pneumoconiosis, emphysema, interstitial pneumonitis, pulmonary fibrosis, tuberculosis, and cancer. Interactions of radon and known or probable human carcinogens in occupational and residential exposure scenarios need to be evaluated for the earlier study groups as well as more recent and current exposed populations. One study of a cohort of uranium miners in the Czech Republic included a finding of significant positive associations between cumulative radon exposures and incidences of chronic lymphocytic leukemia and all leukemias combined (Řeřicha et al. 2006). Additional studies of occupationally- and residentially-exposed individuals are needed to more completely assess the potential for radon-induced leukemias. To a large extent, other health effects have not been studied; additional studies assessing health effects other than cancer do not appear necessary.

Numerous residential case-control studies are available for which possible associations between lung cancer and residential radon levels have been assessed. Collectively, these studies provide evidence of radon-induced lung cancer from long-term residential exposure. Continued assessment of residential radon exposure should include improved methods such as glass-based retrospective radon detectors (Field et al. 1999b; Steck et al. 2002; Sun 2008) and validation of such methods to more accurately estimate exposure scenarios. In addition, extensive data regarding radon exposure in non-residential and residential buildings that use radon-emitting building materials (e.g., natural stone counter tops, floors, and heat sinks) are needed.

Although radon dissolved in drinking water is a source of human exposure, few studies have reported on the potential health implications associated with ingested radon and radon progeny. However, additional studies do not appear necessary at this time.

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Genotoxicity. The genotoxicity of alpha radiation from radon and radon progeny has been investigated in underground miners, in individuals residing in homes with measured radon levels, in laboratory animals *in vivo*, and in a variety of *in vitro* test systems. Increases in chromosomal abnormalities have been reported in peripheral blood lymphocytes of underground miners and occupants of residences where relatively high levels of radon were measured. Results of numerous *in vivo* and *in vitro* studies support the findings of radiation-induced chromosomal abnormalities associated with exposure to radon and radon progeny. Additional studies do not appear necessary at this time.

Reproductive Toxicity. Results of a few epidemiological studies indicated that exposure to radon and its progeny during uranium mining may be associated with alterations in the secondary sex ratio among offspring (Dean 1981; Muller et al. 1967; Wiese and Skipper 1986). More recent assessments of mining cohorts did not focus on reproductive end points. Limited animal data are available regarding potential reproductive effects following exposure to radon and radon progeny. Available toxicokinetic data do not implicate reproductive tissues as particularly vulnerable tissues of concern following exposure to radon and radon progeny.

Developmental Toxicity. Available information regarding the potential for radiation-induced developmental effects following exposure to radon and radon progeny is limited to negative findings in rats following inhalation exposure to 12 WLM of radon and radon progeny (absorbed onto ore dust) for 18 hours/day at a rate of 124 WLM/day on gestation days 6–19 (Sikov et al. 1992). Additional animal studies could be designed to support or refute the results of Sikov et al. (1992).

Immunotoxicity. No information was located regarding potential radon-induced effects on the immune system of humans or in animals exposed to radon and its progeny at concentrations considered relevant to human health.

Neurotoxicity. Cells and tissues in the nervous system may be less radiosensitive, due to a lack of cell turnover or cellular regeneration, than faster regenerating cells of the gastrointestinal tract or pulmonary epithelium. Consequently, neuronal impairment as a result of radon alpha emissions is not expected. Therefore, studies that specifically or directly measure either pathological or functional damage to the nervous system following exposure to radon do not appear to be necessary at this time.

Epidemiological and Human Dosimetry Studies. Knowledge of the adverse health effects in occupationally-exposed humans following chronic-duration exposure to radon and its progeny is based on

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studies in primarily adult male underground miners. These studies describe predominantly respiratory end points, such as pneumoconiosis, emphysema, interstitial pneumonitis, pulmonary fibrosis, tuberculosis, and cancer. However, lung cancer is the only respiratory effect that has been clearly associated with exposure to radon and radon progeny. One study of a cohort of uranium miners in the Czech Republic included a finding of significant positive associations between cumulative radon exposures and incidences of chronic lymphocytic leukemia and all leukemias combined (Řeřicha et al. 2006). Additional studies of occupationally- and residentially-exposed individuals could be of benefit in assessing the potential for radon-induced leukemias; however, such studies would need to include large numbers of subjects given the low incidences of leukemias observed in available studies of radon. To a large extent, other health effects have not been either reported or studied; additional studies assessing health effects other than respiratory and cancer end points do not appear necessary.

Numerous residential case-control studies are available for which possible associations between lung cancer and residential radon levels have been assessed. Collectively, these studies provide evidence of radon-induced lung cancer from long-term residential exposure. Continued monitoring of residential radon exposure is needed to more completely characterize exposure-response relationships. These assessments should include improved methods such as glass-based retrospective radon detectors (Field et al. 1999b; Steck et al. 2002; Sun 2008) and validation of such methods to more accurately estimate exposure scenarios. In addition, extensive data regarding radon exposure in non-residential buildings are needed.

Biomarkers of Exposure and Effect.

Exposure. Potential biomarkers of exposure may include the presence of radon progeny in urine, blood, bone, teeth, or hair. Although the detection of radon progeny in these media is not a direct measurement of an exposure level, estimates may be derived from mathematical models. Quantification of exposure to radon is further complicated by the fact that radon is a ubiquitous substance and background levels of radon and radon progeny are needed to quantify higher than “average” exposures.

Effect. It has been reported that chromosome aberrations in the peripheral blood lymphocytes may be a biological dose-response indicator of radiation exposure (Bilban and Jakopin 2005; Brandom et al. 1978; Pohl-Rüling et al. 1976; Smerkovsky et al. 2001, 2002). In addition, the frequency of abnormalities in sputum cytology has been utilized as an early indicator of radiation damage to lung tissue (Band et al. 1980); this has not been recommended regarding exposure to radon. However, more extensive research is

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needed in order to correlate these effects with radon exposure levels and subsequent development of lung cancer or other adverse effects.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of inhaled and ingested radon and radon progeny has been fairly well studied, but information regarding the toxicokinetics of radon and radon progeny following dermal exposure is limited. Additional information on the deposition patterns in airways for radon progeny and the relationship of these deposition patterns to the onset of respiratory disease could help to enhance understanding of the disease process and delineate health protective measures to reduce deposition.

Comparative Toxicokinetics. Similar target organs have been identified in both humans and laboratory animals exposed to radon and radon progeny. More information on respiratory physiology, target cells, lung deposition, and absorption of radon and its progeny in different animal species is needed to clarify observed differences in species-sensitivity and tumor types. For example, rats generally develop lung tumors in the bronchioalveolar region of the lung while humans develop lung tumors in higher regions (tracheobronchial area). These studies could identify the appropriate animal model for further study of radon-induced adverse effects, although differences in anatomy and physiology of the respiratory system between animals and humans require careful consideration. Most of the information available on the toxicokinetics of radon and progeny has been obtained from studies of inhalation exposure. Studies on the transport of radon and progeny following oral and dermal exposures would be of use for comparing different routes of exposure, although oral and dermal exposure routes do not appear to be of particular toxicity concern.

Methods for Reducing Toxic Effects. Lung cancer is generally considered to be the only toxicity concern following long-term exposure to radon and radon progeny. The high-energy alpha emissions from radon progeny deposited in the lung are the source of toxicity concern. The sequence of events leading from irradiation of living cells is generally believed to involve ionization that causes cellular damage that includes DNA breakage, accurate or inaccurate repair, apoptosis, gene mutations, chromosomal change, and genetic instability. Cigarette smoke, crystalline silica dust, and arsenic have been reported to interact with radon and its progeny to potentiate their effects. The quality of breathing air in mines was addressed decades ago and the concentrations of radon, its progeny, silica dust, arsenic, and other mine pollutants that contribute to lung cancer were effectively reduced.

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Methods for reducing the potential for radon-induced toxic effects consist of reducing or eliminating smoking, as well as periodically testing for radon in indoor air and reducing radon concentrations to below the EPA recommended action level of 4 pCi/L, using active soil depressurization (ASD) in existing homes and radon-reducing features in new home construction. In some cases, an active soil pressurization system (ASP) may be necessary (see Section 6.5 for explanatory information regarding ASD and ASP systems. Laws are being enacted to eliminate or limit smoking in public areas and business locations. Continued research is needed to develop effective smoking reduction and stop smoking campaigns and to develop and implement additional techniques for reducing radon levels in homes and public buildings.

Children's Susceptibility. If data needs, relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are identified, they are discussed in detail in the Developmental Toxicity subsection above.

Age-related differences in susceptibility to the effects of exposure to radon and radon progeny have not been demonstrated. Differences in lung morphometry and breathing rates in children may result in higher estimated radiation doses relative to adults (NCRP 1984a; Samet et al. 1989). However, available information from children employed as miners in China does not provide evidence of increased susceptibility to the effects of exposure to radon (Lubin et al. 1990; NIH 1994).

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Additional research known to be underway includes pooling of results from Iowa and Missouri residential radon studies using glass-based detectors that are undergoing final calibration (Field, personal communication) and pooling of results from the residential radon studies that contributed to the results of Lubin et al. (2004; China studies), Krewski et al. (2005, 2006; North American studies) and Darby et al. (2005, 2006; European studies).