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 of the short half-life of ^{220}Rn (56 seconds). 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 ($3.7x10^{10}$ transformations per second). In discussing radon, a smaller unit, the picocurie (pCi), is used, where 1 pCi=$1x10^{-12}$ 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/m^3 of air. One pCi/L is equivalent to 37 Bq/m^3. 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 fore some time, and some excretion occurs, the term dose refers specifically to the amount of radiant energy absorbed in a particular tissue or organ and is expressed in rad (or grays).

When radon and its progeny decay, they emit alpha and beta particles as well as gamma radiation. 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 radium transforms to radon, the alpha particles are neutralized to form stable helium (He); the charged decay product particles 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 attached and unattached fractions of radon progeny are inhaled, deposit in the airway (particularly the tracheobronchial tree), and bombard nearby cells with alpha particles as the atoms transform through the decay chain. These alpha particles can deliver a large localized radiation dose. 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.

Because it is not feasible to routinely measure the activities of individual radon progeny in the environment, a unit termed the "Working Level" (WL) is used for the purpose of quantifying exposure to radon and its radioactive progeny. 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, $^{222}Rn(\alpha)\rightarrow {}^{218}Po(\alpha)\rightarrow {}^{214}Pb\rightarrow {}^{214}Bi\rightarrow {}^{214}Po(\alpha)\rightarrow {}^{210}Pb$, 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 $1.3x10^5$ million electron volts (MeV) of alpha energy during decay. One WL is equivalent to the potential alpha energy of $2.08x10^5$ joules in 1 cubic meter of air (J/m^3).

To convert between units of ^{222}Rn radioactivity (pCi or Bq) and the potential alpha energy concentration (WL or J/m^3), the equilibrium between radon gas and its progeny must be known or assumed (see Chapter 10 for conversion formula). When radon is in 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). However, when removal processes other than radioactive decay are operative, such as with room air ventilation, 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 (37 Bq/m^3) of radon in the air is approximately equivalent to 0.004 WL of radon progeny.

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 J-hour/m^3; 1 WLM=$3.6x10^3$ J-hours/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 of radon gas. 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 0.004 WL of radon progeny (EPA 2003; NAS 1999a). These conditions result in the following relationship:

1 pCi/L x 0.004 WL/pCi x 0.7 x (8,760 hours/WL-year ÷ 170 hours/WL-M) = 0.144 WL-M/year

Because 1 pCi/L is equivalent to 37 Bq/m^3, a residential exposure scenario using equivalent assumptions to those described above results in the same cumulative exposure to radon progeny (0.114 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 (^{222}Rn) is 3.8 days. The radioactive decay of radon to ^{218}Po (radiological half-life=3.05 minutes) is accompanied by the release of high-energy (5.5 MeV) alpha particles; decay of ^{218}Po to lead-214 (^{214}Pb; radiological half-life=26.8 minutes) also releases high-energy (6.0 MeV) alpha particles. Subsequent radioactive decay to bismuth-214 (^{214}Bi; radiological half-life=19.7 minutes) and ^{214}Po 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 ^{214}Po via release of high-energy (7.69 MeV) alpha particles occurs so rapidly (radiological half-life=1.6×10^{-4} seconds) that, in radiation dose modeling, these alpha emissions are generally attributed to ^{214}Bi decay (i.e., the rate of decay of ^{214}Bi is essentially equal to the rate of formation of ^{210}Pb due to the essentially instantaneous decay of ^{214}Po from ^{214}Bi). The subsequently-formed radioactive radon progeny (^{210}Pb, ^{210}Bi, and ^{210}Po 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 ^{210}Pb is 21 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 ^{218}Po and ^{214}Po (due to the rapid decay of these alpha emitters).

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, 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).

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, 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 a defined geographic region.

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 radon exposure levels in the working environment and inherent uncertainty due to confounding factors such as smoking status and coexposure to known or suspected human carcinogens (diesel exhaust, arsenic, and silica dust), 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.

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. 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, whereas no consistent associations were observed in others. None of the available residential case-control studies 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. The individual residential case-control studies typically employed relatively low numbers of cases and matched controls, which limits the statistical power of a particular 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 measurement error and residential mobility. In order to more precisely estimate risk, most of the investigators have pooled data from their studies. The pooled analyses have found statistically significant, positive associations between lung cancer and residential radon levels.

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. Results of available ecological studies assessing possible associations between environmental radon levels and lung cancer incidence are mixed; both positive and negative associations, as well as no significant associations, have been suggested. Several ecological studies have indicated positive associations between radon levels and selected leukemias. 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. 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.

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. Assessments did not necessarily include adjustments for confounding exposures to arsenic, silica dust, 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 1999b; 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, 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% confidence interval [CI] 0.002–0.025) for exposures <50 WLM and 0.0080/WLM (95% CI 0.003–0.014) for exposures <100 WLM.

Assessments of pooled data from major residential case-control studies include 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 individual case-control studies that contributed to the combined analysis of North American case-control studies were performed in regions of New Jersey, 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 with a majority 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

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]

		Follow-up		Non-exposed workers		Exposed workers and mean cumulative WLM		
Study cohort	Mine type	Period	Length (years)	Number	Person-years	Number	Person-years	WLM
China	Tin	1976–1987	10.2	3,494	39,985	3,494	39,985	277.4
Czech Republic	Uranium	1952–1990	25.2	0	4,216	0	4,216	198.7
Colorado	Uranium	1950–1987	24.6	0	7,403	0	7,403	807.2
Ontario	Uranium	1955–1986	17.8	0	61,017	0	61,017	30.8
Newfoundland	Fluorspar	1950–1984	23.3	337	13,713	337	13,713	367.3
Sweden	Iron	1951–1991	25.7	0	841	0	841	80.6
New Mexico	Uranium	1943–1985	17.0	12	12,152	12	12,152	110.3
Beaverlodge	Uranium	1950–1980	14.0	1,591	50,345	1,591	50,345	17.2
Port Radium	Uranium	1950–1980	25.2	683	22,222	683	22,222	242.8
Radium Hill	Uranium	1948–1987	21.9	1,059	26,301	1,059	26,301	7.6
France	Uranium	1948–1986	24.7	16	4,556	16	4,556	68.7
Totals[b]			17.2	7,176	242,332	7,176	242,332	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]	

[a]Table entries include 5-year lag interval for radon progeny exposure.
[b]Totals adjusted for 115 workers (including 12 lung cancer cases) who were included in both New Mexico and Colorado cohorts.
[c]Mean WLM among exposed miners is 160.2.
[d]Adjusted for cohort, age, other occupational exposures, and ethnicity.

CI = confidence interval; WLM = working level months

Source: NIH 1994

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)

[a]The 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).
[b]Table entries include 5-year lag interval for radon progeny exposure.
[c]Totals adjusted for 115 workers (including 12 lung cancer cases) who were included in both New Mexico and Colorado cohorts.
[d]Adjusted 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

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 3-3, along with odds ratios (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. Excess odds ratios (EORs) were 0.10 per 100 Bq/m^3 (95% CI -0.1–0.28) for the unrestricted dataset and 0.18 per 100 Bq/m^3 (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 3-3).

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. Results of this analysis provide additional evidence of an association between residential radon and lung cancer risk. This evidence includes statistically significant relative risks at exposure concentrations ≥400 Bq/m^3 (10.8 pCi/L), an ERR of 0.084 per 100 Bq/m^3 (95% CI 0.03–0.158) for the full range of observed radon concentrations, and ERRs of 0.140 per 100 Bq/m^3 (95% CI 0.004–0.309) for exposure concentrations <200 Bq/m^3 (<5.4 pCi/L), 0.095 per 100 Bq/m^3 (95% CI 0.005–0.206) for exposure concentrations <400 Bq/m^3 (<10.8 pCi/L), and 0.078 per 100 Bq/m^3 (95% CI 0.012–0.164) for exposure concentrations <800 Bq/m^3 (<21.6 pCi/L) (Table 3-4).

Although the dose-response coefficients from the mining studies and residential studies are expressed in different units of exposure (i.e., WLM vs. Bq/m^3), they can be compared by applying the relationship described above, namely that 1 pCi/L (37 Bq/m^3) is equivalent to 0.144 WLM/year. Thus, a 25-year exposure at 200 Bq/m^3 (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/m^3. This

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

	Number of subjects		Time-weighted average radon concentration in Bq/m^3		
Region	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

Odds ratios for lung cancer

Radon concentration		Number of subjects		Odds ratio[a]
Bq/m^3	pCi/L	Cases	Controls	(95% confidence interval)
<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 odds ratio (β)=0.10 per 100 Bq/m^3 (95% confidence interval -0.01–0.28)[b]				

Odds ratios 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		Odds ratio[a]
Bq/m^3	pCi/L	Cases	Controls	(95% confidence interval)
<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 odds ratio (β)=0.18 per 100 Bq/m^3 (95% confidence interval 0.02–0.43)[b]				

[a]Odds ratios 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.
[b]Based on linear model: $OR(x)=1+\beta x$, where x is the radon concentration in the exposure time window.

Source: Krewski et al. 2006

Table 3-4. 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 (-0.192–306)
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

value is similar to the estimates for excess relative risk (0.084/Bq/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 Bq/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.

Animal studies derive mainly from 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, ethnicity, smoking history, and work experience were likely major contributors to mortalities from noncancer respiratory diseases. Mortality due to nonneoplastic respiratory diseases was not significantly elevated in other studies of mining cohorts. 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. 2004) or Newfoundland fluorspar miners (Villeneueve et al. 2007a).

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). No additional animal studies were located for which exposure levels were considered relevant to human health.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, hepatic, dermal, body weight, or ocular 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 pneumoconioses, emphysema, interstitial pneumonitis, pulmonary fibrosis, and tuberculosis (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 was likely a major contributor to mortalities from noncancer respiratory diseases. 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).

Alterations in respiratory function in U.S. uranium miners have been reported (Archer et al. 1964; Samet et al. 1984a; Trapp et al. 1970). Analyses among U.S. uranium miners indicated decrements in pulmonary function with increasing cumulative exposure (Archer et al. 1964) and with the duration of underground mining (Samet et al. 1984a). Evaluations of these respiratory end points did not permit

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. 2004) or Newfoundland fluorspar miners (Villeneueve et al. 2007a).

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 (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.

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).

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; Checkoway et al. 1985; Gottlieb and Husen 1982; Hornung and Meinhardt 1987; Hornung et al. 1998; Lubin et al. 1995a, 1995b, 1997; 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; 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 (Ševc et al. 1988, 1993; Tomášek 2002; 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 (Laurier et al. 2004; Leuraud et al. 2007; Rogel et al. 2002; Tirmarche et al. 1993; Vacquier et al. 2007), Germany (Brüske-Hohlfeld et al. 2006; Kreuzer et al. 2000; Taeger et al. 2006), Italy (Carta et al. 1994), Norway (Solli et al. 1985), and Sweden (Axelson and Sundell 1978; Damber and Larsson 1982; Edling and Axelson 1983; 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. The results of these studies consistently demonstrate increased risk of mortality from lung cancer with increasing WLM (see Table 3-2). Lubin et al. (1997) provide the most recent report of pooled results from eleven of these cohorts. The pooled 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. Restricting exposed miner groups by cumulative exposure (<50 and <100 WLM) resulted in 353 and 562 lung cancer deaths, 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). ERRs (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. 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.

Some studies of mining cohorts examined mortality from cancers other than lung cancer. Results of a few of these studies indicate slight excessive mortalities from laryngeal, liver, kidney, and/or gall bladder cancers (Kreuzer et al. 2004; Tirmarche et al. 1992; Tomášek et al. 1993; Vacquier et al. 2007); however, these slight excesses did not appear to be related to cumulative exposure to radon and were not found in excess in other studies of mining cohorts.

The results of the miner studies consistently demonstrate significant positive associations between lung cancer and exposure to radon. However, it must be noted that potential confounding by silica dust inhalation (identified as a known human carcinogen in the 11th Report on Carcinogens subsequent to most reports of the miner cohorts [NTP 2005b]) might influence the calculated impact of radon on lung cancer mortality in the mining cohorts. Statistically significant excess lung cancer mortality was associated with average cumulative exposures 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. 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). 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 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). In a subcohort of 516 white nonsmoking uranium miners (drawn from a larger cohort of U.S. uranium miners), mean exposure was reportedly 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. No lung cancer deaths were found in nonsmoking miners who had exposure <465 WLM (Roscoe et al. 1989).

Most of the reported epidemiological studies of uranium mining cohorts did not find significant associations between radon exposure and cancers other than lung cancer (Kreuzer et al. 2004; Laurier et al. 2004; Möhner et al. 2006; Roscoe 1997; Tomášek et al. 1993). Řeřicha et al. (2006) reported significant positive associations between cumulative radon exposures and incidences of chronic lymphocytic leukemia (relative risk [RR]=1.75; 95% CI 1.10–2.78) and incidences of all leukemias combined (RR=1.98; 95% CI 1.10–3.59) in a cohort of Czech uranium miners at 110 WLM. However, statistically significant associations between radon exposure and leukemias have not been found by other investigators of uranium mining cohorts.

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, Isreal, Italy, Japan, 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 major residential case-control studies, a combined analysis of seven 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). 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 and 3-4), including a statistically significant relative risk of lung cancer at mean radon concentrations ≥542 Bq/m^3 (14.65 pCi/L) reported by Darby et al. (2006) (Table 3-4).

Assessment of the results of residential case-control studies and comparisons between the presently-available pooled results of the North American case-control studies (Krewski et al. 2005, 2006) and the 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 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.

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 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

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

3.2.3.1 Death

3.2.3.2 Systemic Effects

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 exposed occupationally for 10 years or more to approximately 3.08 pCi/L of air ($1.74x10^2$ Bq/m^3) resulting in 6.22 pCi (0.23 Bq) radon/cm^2 skin surface area (Ševcová et al. 1978). Exposure to other agents 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.

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

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 3-5 and 3-6 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

Table 3-5. 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
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
Rat (bone marrow)	Sister chromatid exchanges	+	Poncy et al. 1980

– = negative result; + = positive result

Table 3-6. 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 (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

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 glycophorin 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/m^2 (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/m^3; 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 found in another small group (n=22) of subjects with residential exposure to radon at concentrations in the range of 50–800 Bq/m^3 (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 irradiation on DNA repair in lymphocytes of persons occupationally exposed to radon (3,000 pCi/L of air [$1.1x10^5$ Bq/m^3]). The study further indicated higher DNA-repair rates in juvenile cells than in fully differentiated cells.

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 $2.9x10^4$–$1.2x10^6$ pCi radon/L

of water ($1.1x10^3$–$4.4x10^4$ 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). Brooks and coworkers (Brooks et al. 1994) 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 (Wolff et al. 1991) and human fibroblasts (Loucas and Geard 1994). 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 (^{4}He) 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 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 the toxicokinetics of radon progeny, which contribute substantially 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 bismuth, lead, and polonium in this profile; the reader is referred to relevant literature on the toxicokinetics of each radionuclide (Agency for Toxic Substances and Disease Registry 2007; ICRP 1980, 1994c). Ultimately, 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 21 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 2007) 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).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhalation exposures to radon gas deliver the gas into the respiratory tract along with aerosols of radon progeny (e.g., ^{214}Bi, ^{214}Pb, ^{218}Po) that form as a result of the progeny reacting with natural aerosols in the air (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 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 unattached fraction for typical indoor environments has been estimated to be 5–20% of the total airborne potential alpha energy concentration (PAEC) (Porstendörfer 1994, 2001). The PAEC gives a measure for the potential energy originating from the alpha decays of radon progeny in air. Smoking and other aerosol-generating activities (e.g., vacuum cleaning, cooking, fireplace and circulating fan usage) will decrease the unattached fraction and 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 and carrier aerosols. Radon is a relatively nonreactive gas, and deposition and absorption will be determined largely by its solubility in tissues 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 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 ^{218}Po was estimated to be 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 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}Po/^{214}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. Absorption of radon progeny following oral exposure is thought to occur largely in the small intestine (Agency for Toxic Substances and Disease Registry 2007; 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 (1995, 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 2007; 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/m^3) compared to pre-bath levels of <1 pCi/L of air (37 Bq/m^3). 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 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 $minute^{-1}$), assuming a blood flow of 0.16 L/minutes 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±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) 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 2007; ICRP 1980, 1994c, 1995). 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 2007). 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 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 2007; 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 2007; ICRP 1980, 1994c, 2001). ICRP (1995, 2001) recommends the following values for the purpose of modeling bismuth-derived radiation doses: a urine:fecal excretion ratio of 1:1 and elimination $t_{1/2}$ values of 0.6 (60% of issue burden) and 5 days (40% of tissue burden) for fast and slow phases, respectively. ICRP (1995, 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}Bi:^{222}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 2007; 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.

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.

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

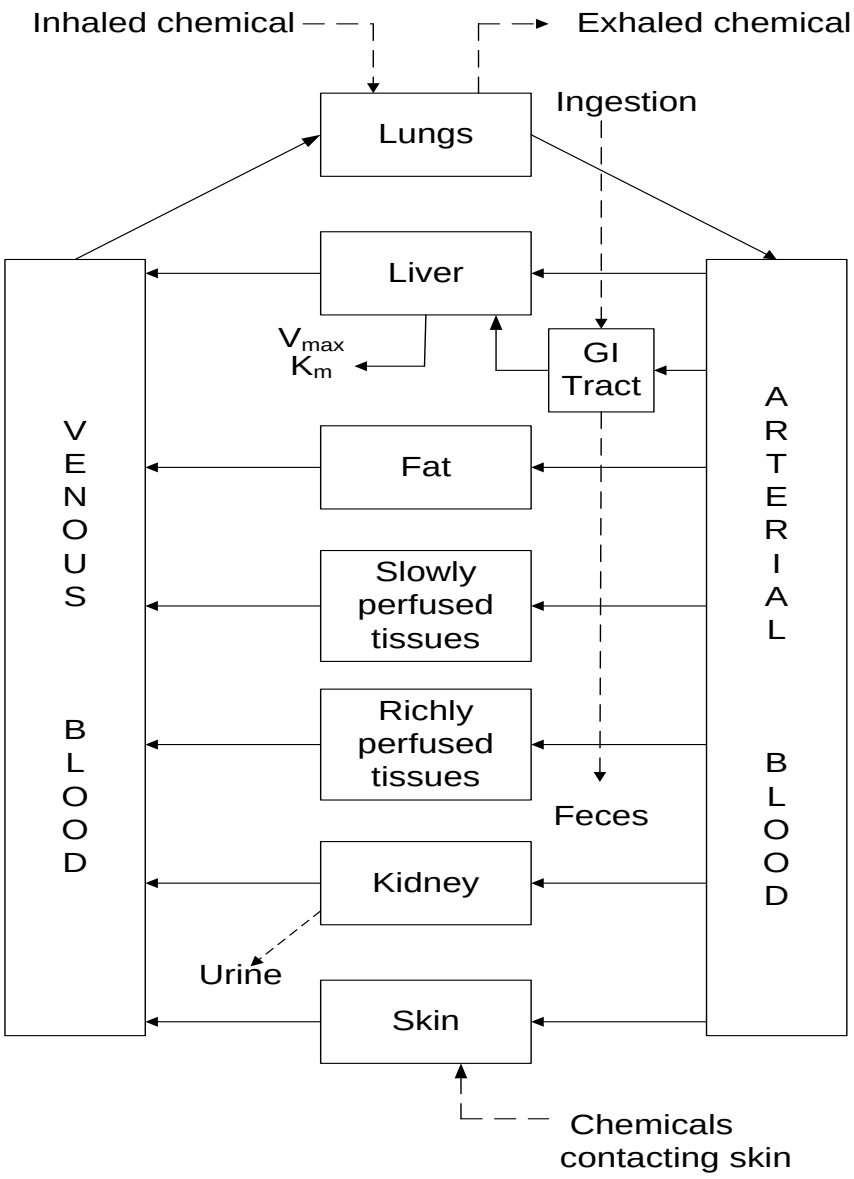
sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-1 shows a conceptualized representation of a PBPK model.

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 3-1 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 developed to simulate radiation doses emanating 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

Figure 3-1. 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

(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 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 2007; ICRP 1979, 1994c, 1995; 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)

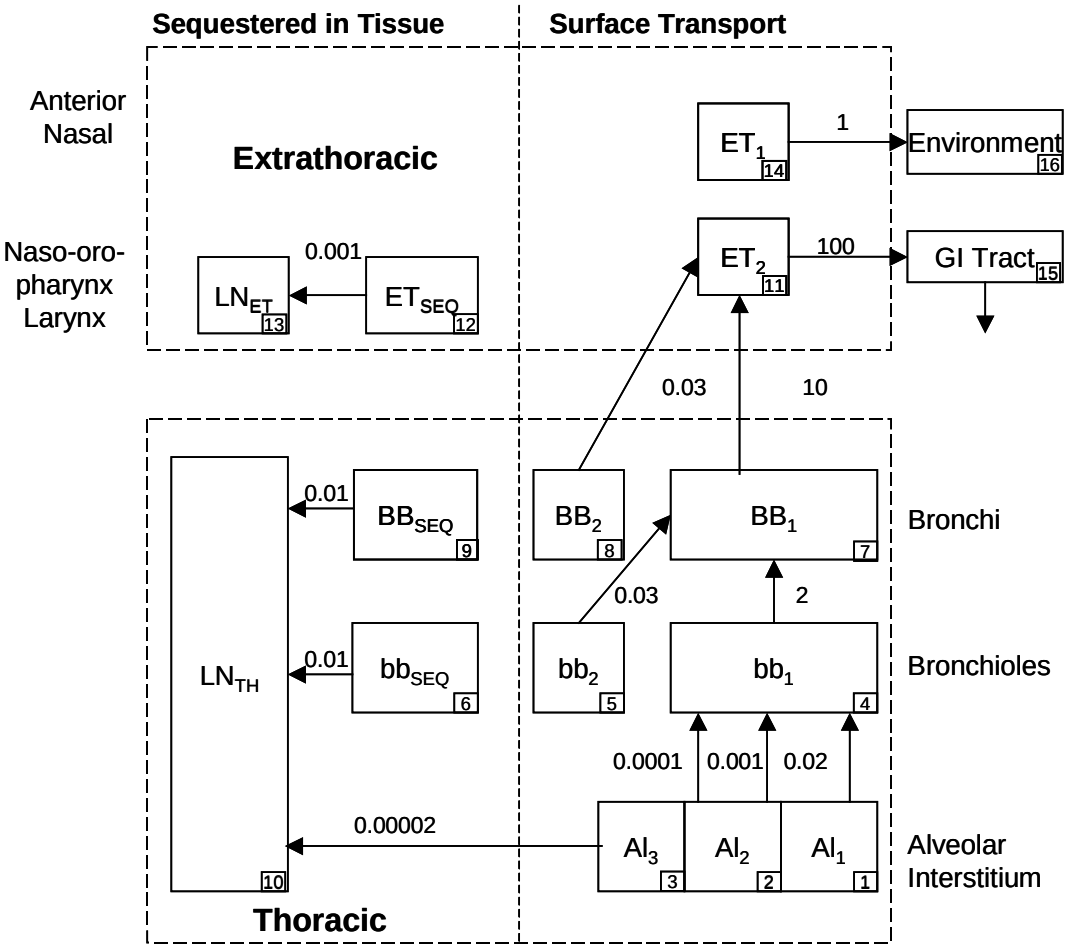
Deposition. The ICRP (1994b) has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region of the respiratory tract. ICRP (1994b) provides inhalation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

The ICRP deposition model estimates the fraction of inhaled material initially retained in each compartment (see Figure 3-2). 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 3-7 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

Figure 3-2. 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 3-8.

Source: ICRP 1994b

Table 3-7. 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($m^3 hour^{-1}$)	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($m^3 hour^{-1}$)	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($m^3 hour^{-1}$)	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($m^3 hour^{-1}$)	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.

respiratory tract (see Figure 3-3). 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.

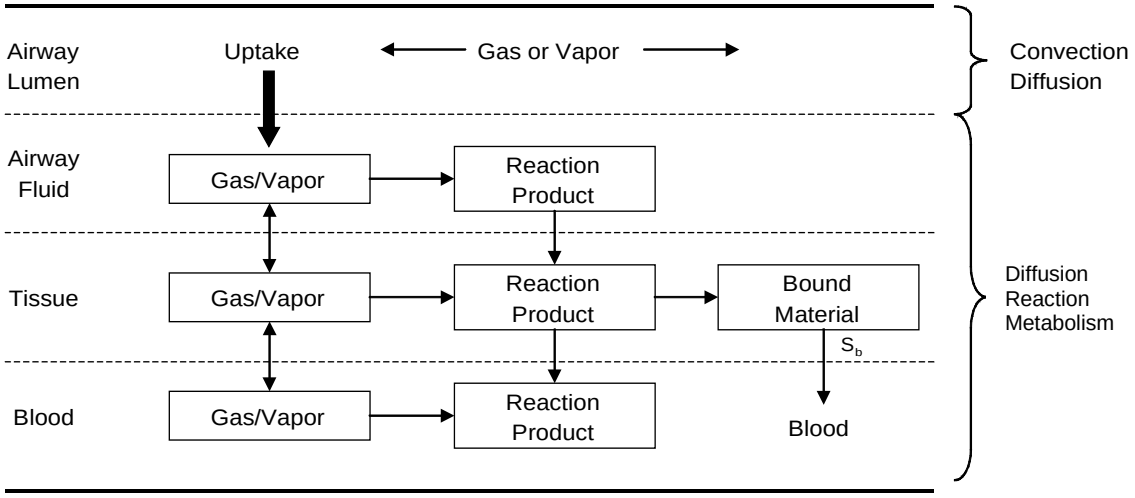
- Type SR-1 compounds include soluble or reactive gases and vapors which are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, 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 (SO_2) 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% ET_1, 20% ET_2, 10% BB, 20% bb, and 40% AI. Radon progeny, such as ^{218}Po, ^{214}Pb, and ^{214}Bi 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

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



Source: ICRP 1994b

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 3-2) with reference values presented in Table 3-8. This table provides 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”

Table 3-8. 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]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	$1x10^{-4}$	7,000 days
$m_{3,10}$	AI_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

Table 3-8. 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
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The 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 AI_3 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 AI_3 is determined by the sum of the clearance rates.
[b]See paragraph 181, Chapter 5 (ICRP 1994b) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

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

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

where
f_s = fraction subject to slow clearance
d_{ae} = aerodynamic particle diameter/(μm)
ρ = particle density (g/cm^3)
χ = particle shape factor

AI = 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

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 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}).

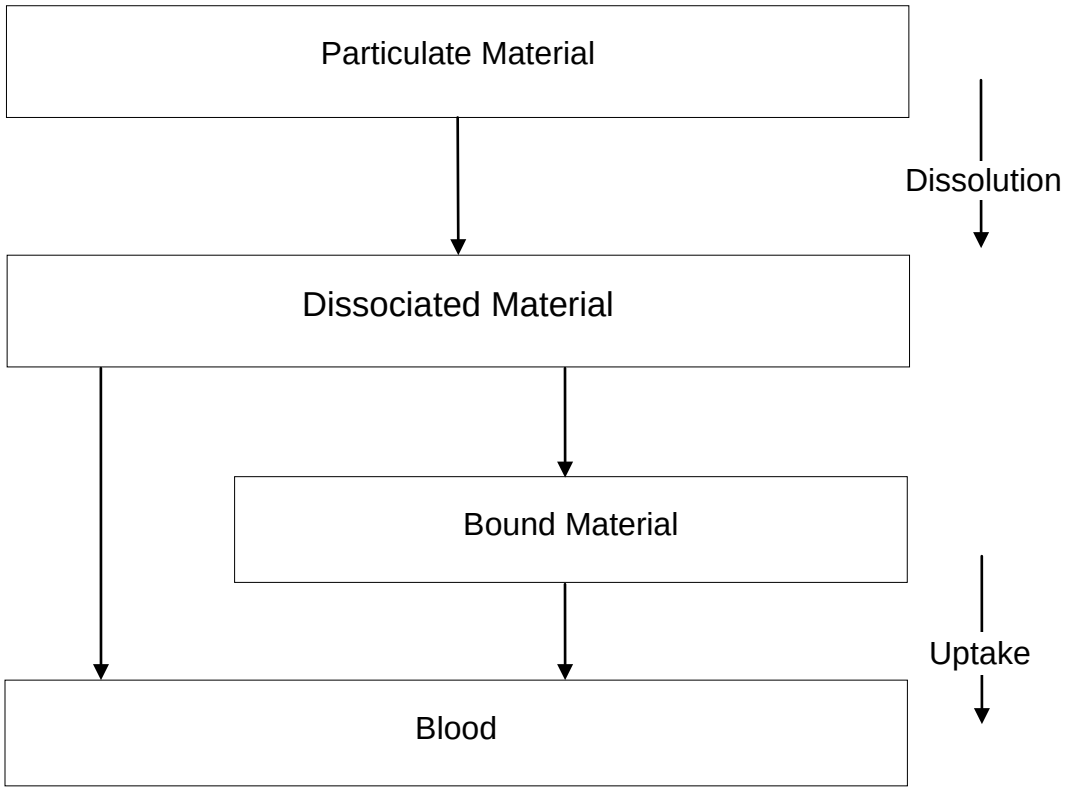
If particles reach and become deposited in the alveoli, they tend to become imbedded in the fluid on the alveolar surface or move into the lymph nodes. Coughing is the one mechanism by which particles are physically resuspended and removed from the AI region. For modeling purposes, the AI region is divided 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 3-4. 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.

Figure 3-4. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994b

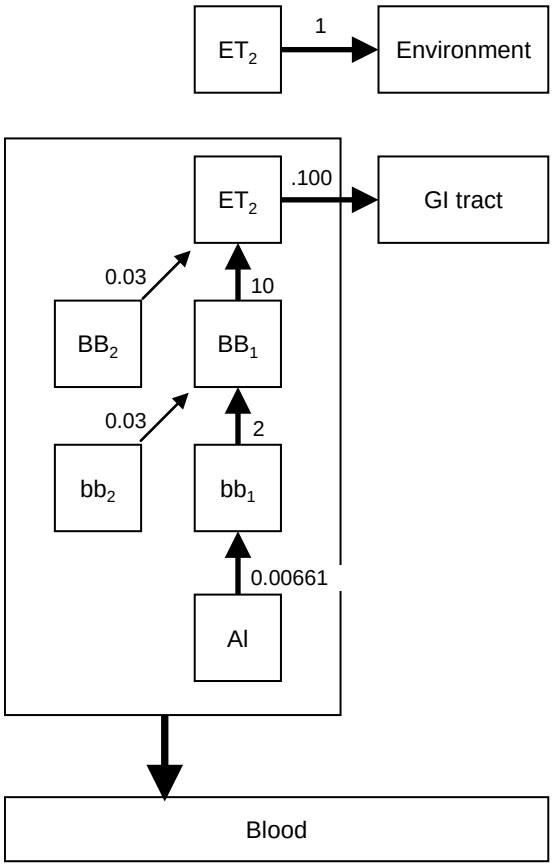
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.

- For Type V, complete absorption (100%) is considered to occur instantaneously.

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^{-1} 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).

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 3-5): (1) the alveolar

Figure 3-5. Simplified Version of the Human Respiratory Tract Model (HRTM)



Source: Marsh and Birchall 2000

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.

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).

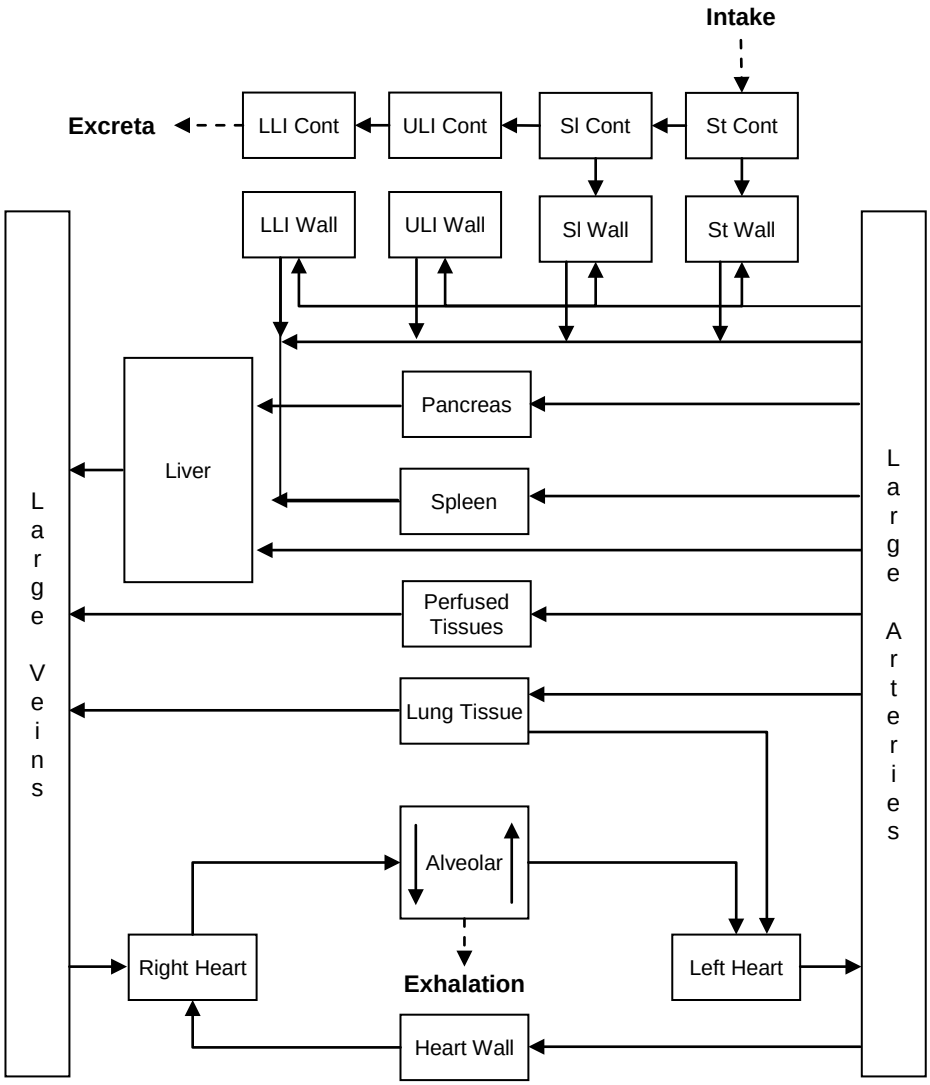
Species Extrapolation. The model is based on both human and animal data. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in modal parameters.

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 radon gas (Figure 3-6). 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 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

Figure 3-6. Schematic Diagram of the NAS (1999b) PBPK Model Developed to Describe the Fate of Radon within Systemic Tissues



Source: NAS 1999b

in the stomach wall of approximately 30% of that of the lumen. Parameter values for adults are presented in Table 3-9. 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 3-7). The model is similar in structure to the NRC (NAS 1999) 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 (1999) 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 blood:tissue partition coefficients (Table 3-10). Values for blood flows were derived from Leggett and Williams (1991, 1995); and tissue volumes were derived from ICRP (1990). Tissue:blood partition

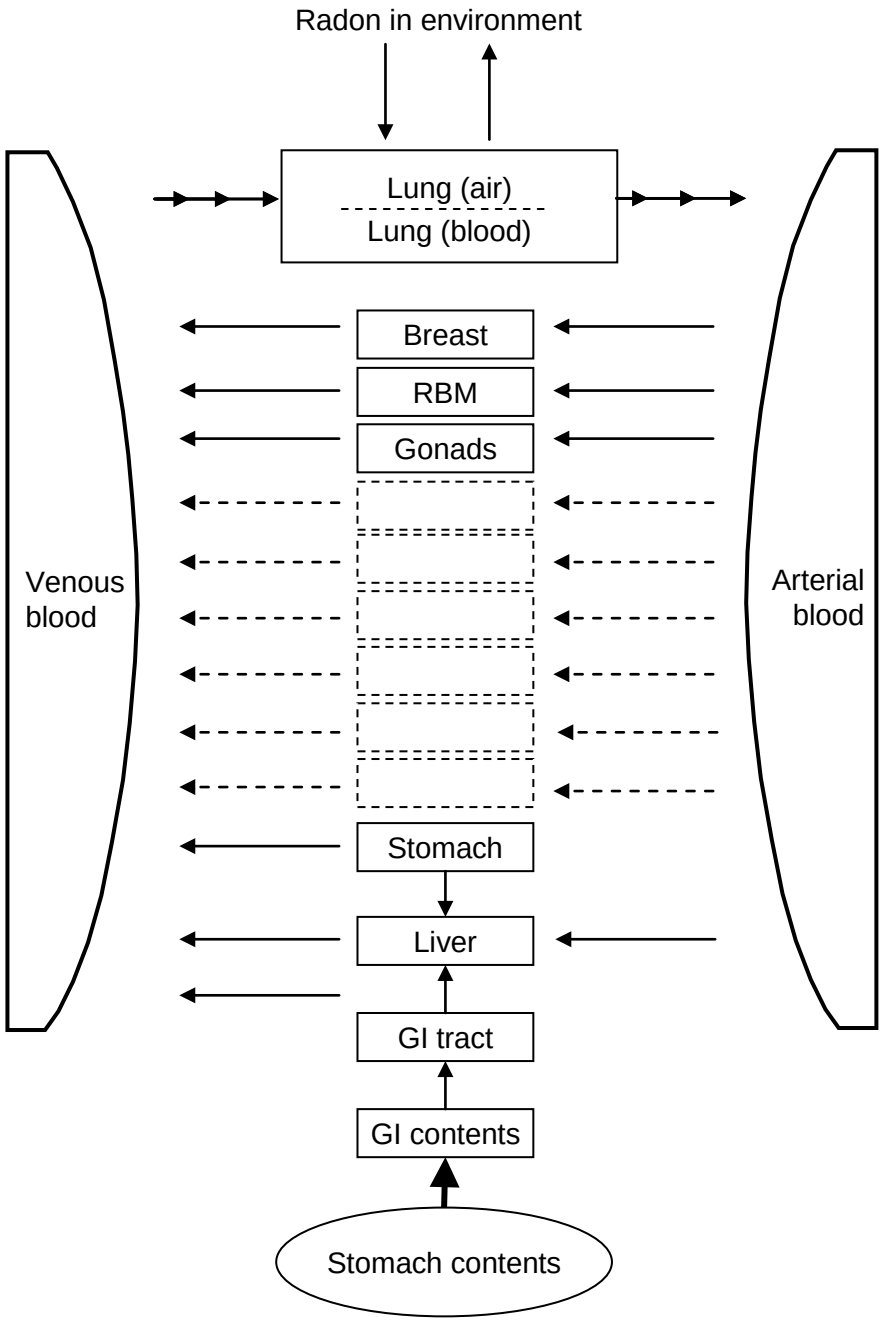
Table 3-9. Parameters in the NAS (1999b) PBPK Model[a]

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

[a]Values shown for physiological parameters (flows, masses, densities) are for adults.

Source: NAS 1999b

Figure 3-7. Khursheed (2000) PBPK Model for Inhalation and Ingestion of Radon Gas



Source: Khursheed 2000

Table 3-10. 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

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/m^3 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}Rn; radioactive half) is a relatively inert noble gas found in air and some deep well water sources. Radon occurs with aerosols of short-lived radioactive progeny (i.e., ^{214}Bi, ^{214}Pb, ^{218}Po) that form as a result of the progeny reacting with natural aerosols in the air and water. Deposition and absorption 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 2007; ICRP 1980, 1994c, 1995). 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 2007; 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, 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

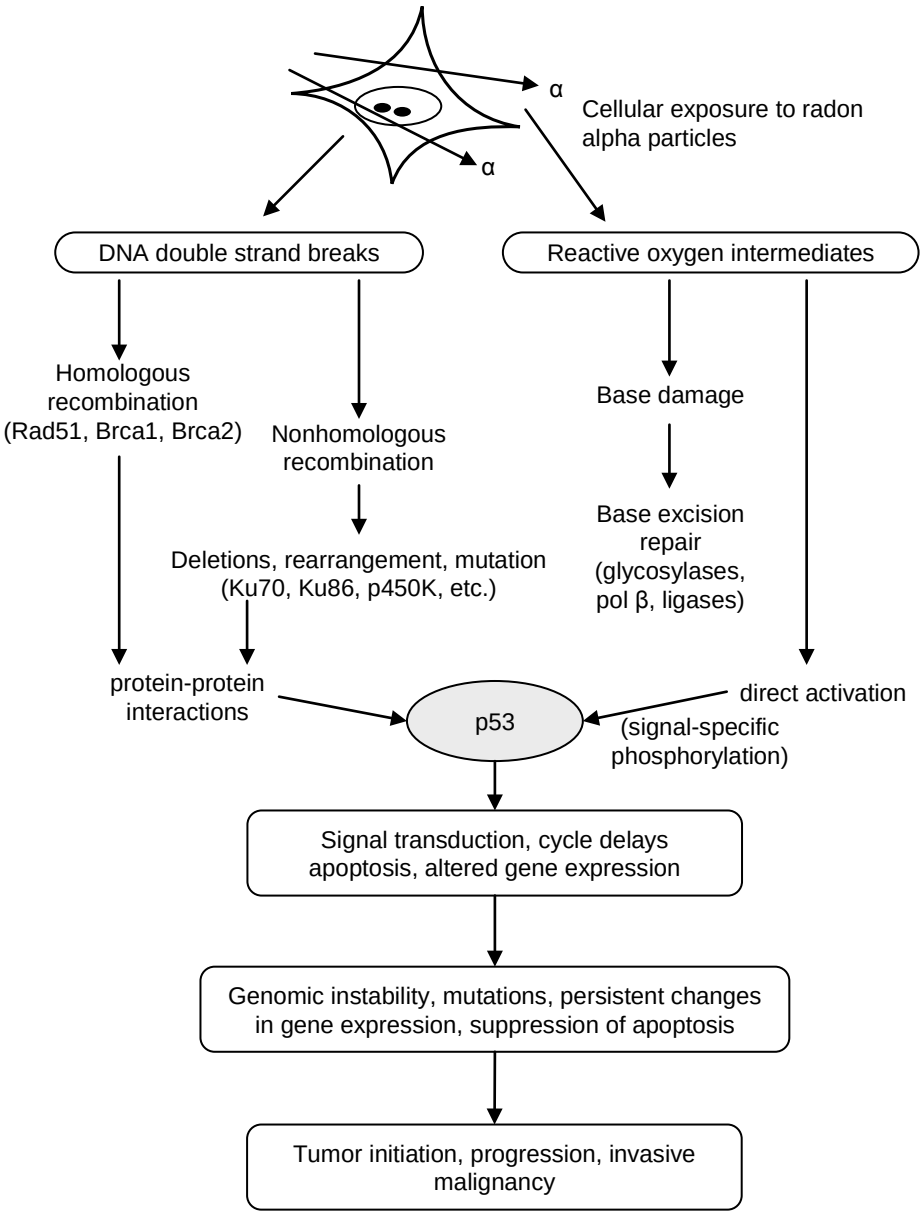
information in this section is summarized predominantly from Chapter 6 (Molecular and Cellular Mechanisms of Radon-Induced Carcinogenesis) of the Risk Assessment of Radon in Drinking Water produced for the National Academy of Sciences (NAS 1999b). The reader is referred to this source for more detailed 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 3-8 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 3-8). 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.

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

Figure 3-8. Conceptual Model of the Biology Leading From Alpha Irradiation of Cells by Radon and Radon Progeny to Tumor Development



Source: NAS 1999b

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/m^3 (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.

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 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 isoflavinoid 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).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to radon or its progeny.

No *in vitro* studies were located regarding endocrine disruption of radon or its 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 chemicals. 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.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (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). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. 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 chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; 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 chemical. 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).

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).

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).

A biomarker of exposure is 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). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites 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. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites 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 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 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 xenobiotic 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.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Radon

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, particularly as a consequence of ingestion of food or water, 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 from levels of stable radon 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. Quantification of exposure to radon is further complicated by the fact that radon is a ubiquitous substance, and background levels of radon and its progeny are needed to quantify higher than "average" exposures.

3.8.2 Biomarkers Used to Characterize Effects Caused by Radon

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). Although abnormal sputum cytology may be observed following radon exposure, this effect is also seen following exposure to other carcinogens such as cigarette smoke. In addition, even though increases in the frequency of abnormal 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; Brandom et al. 1978; Smerhovsky et al. 2001, 2002) and increased frequency of mutations of glycophorin A in blood (Shanahan et al. 1996). However, these genotoxic effects can not be exclusively attributed to exposure to radon and its progeny.

3.9 INTERACTIONS WITH OTHER CHEMICALS

The interaction of cigarette smoke with radon and the possible effect on radon-induced toxicity is a complex one and is still an issue under consideration. 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). Studies by Lundin et al. (1969, 1971) reported 10 times more lung cancer among U.S. uranium miners who smoked. In a case-control study of U.S. uranium miners, Archer (1985) reported that smoking miners with lung cancer had significantly reduced latency- induction periods than nonsmokers. Cigarette smoking also appeared to shorten the latency period for lung cancer among Swedish lead-zinc miners (Axelson and Sundell 1978) and Swedish iron miners (Damber and Larsson 1982). Miners who smoke cigarettes may be at higher risk because of possible synergistic effects between radon and its progeny and cigarette smoking (Klaassen et al. 1986). For example, modeling results of Thomas et al. (1994), using data on lung cancer mortality in the Colorado Plateau uranium mining cohort, indicated a multiplicative synergistic relationship between lung cancer mortality and exposure to radon among smokers. The strongest modifier of the synergistic effect between radon and smoking in this cohort was the timing of exposures. Exposure to radon followed by the onset of smoking resulted in a more-than-multiplicative effect, whereas when smoking was initiated prior to occupational radon exposure, the synergistic effect was sub-multiplicative. 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. Results of analysis of pooled results from 13 European residential case-control studies indicate that the proportionate increase in lung cancer risk per unit increase in radon concentration is similar in lifelong nonsmokers and cigarette smokers. At

the level of the individual, radon-induced lung cancer risk following exposure to radon concentrations up to 400 Bq/m^3 (10.8 pCi/L) is thought to be approximately 25 times greater than the risk for cigarette smokers (Darby et al. 2005, 2006).

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.

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 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), 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. 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).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Populations that may be more susceptible to the respiratory effects of radon and its progeny are people who have chronic respiratory disease, such as asthma, emphysema, or fibrosis. People with chronic respiratory disease 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). Therefore, radon and its progeny would be resident in the lungs for longer 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 (Morken 1973). In an assessment of lung cancer cases pooled from three residential case-control studies, radon concentrations >121 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 had been 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 and its 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.

Methods for reducing the potential for radon-induced toxic effects consist of monitoring indoor air for radon levels, reducing potentially hazardous levels by ventilation and other accepted radon removal methods, and cessation of cigarette smoking.

3.11.1 Reducing Peak Absorption Following Exposure

No data are available.

3.11.2 Reducing Body Burden

No data are available.

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. 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.

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.

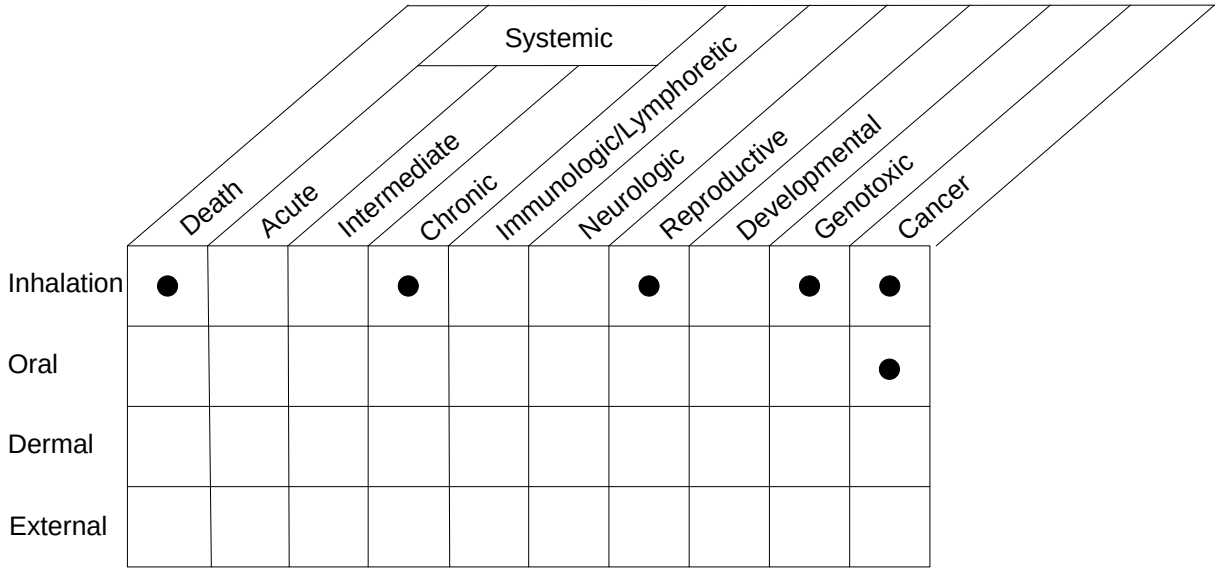
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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

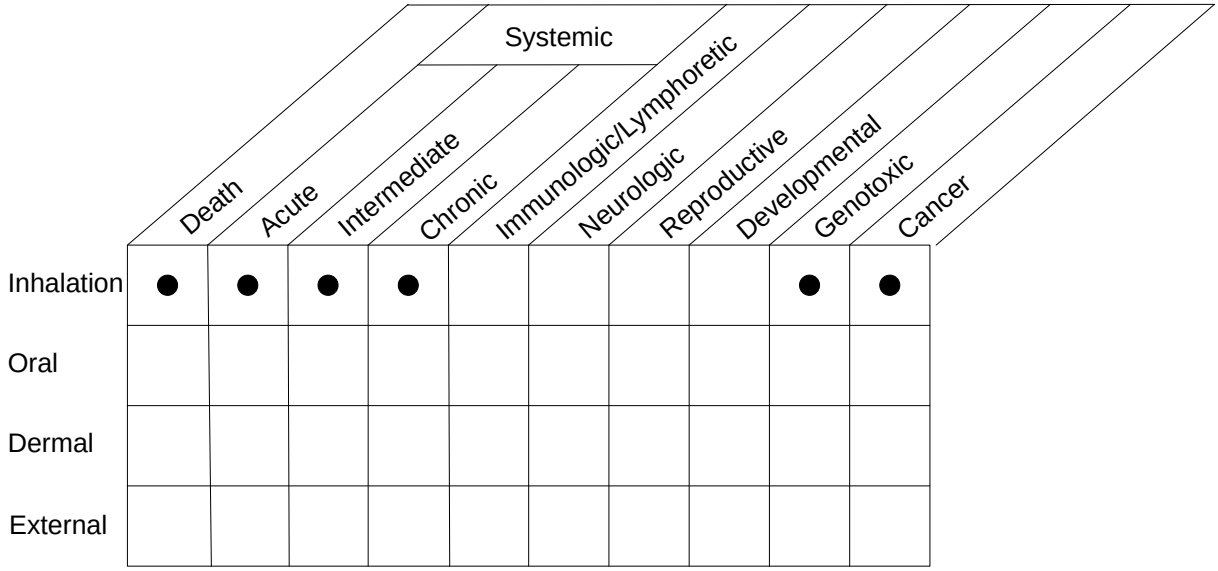
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to radon are summarized in Figure 3-9. The purpose of this figure is to illustrate the existing information concerning the health effects of radon. Each dot in the figure indicates that one or more studies 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. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-9 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

Figure 3-9. Existing Information on Health Effects of Radon



Human



Animal

● Existing Studies

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 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. 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 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 assessment of residential radon exposure is needed to more accurately assess health risks associated with long-term residential exposure to radon and radon progeny. 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.

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.

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 destation 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 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 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 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 (Brandom et al. 1978; Pohl-Rüling et al. 1976) that chromosome aberrations in the peripheral blood lymphocytes may be a biological dose- response indicator of radiation exposure. 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). However, more extensive research is 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 appears to interact with radon and its progeny to potentiate their effects.

Methods for reducing the potential for radon-induced toxic effects consist of monitoring indoor air for radon levels, reducing potentially hazardous levels by ventilation and other accepted radon removal methods, and cessation of cigarette smoking.

There are no known methods for reducing peak absorption or body burden of radon progeny. There is some indication that diets high in fruits and vegetables might be of benefit in neutralizing reactive oxygen species produced by cigarette smoke and radon (see Alavanja 2002).

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.

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

The following ongoing studies were identified in the Federal Research in Progress database (FEDRIP 2008).

Dr. Martha Linet, from the National Cancer Institute Division of Cancer Epidemiology and Genetics, is assessing the modification of risk from smoking intensity using tobacco data from a comprehensive case-control study of lung cancer in rural China in which high indoor radon levels were associated with increased risk of lung cancer.

Dr. David Mendez, from the University of Michigan, is modifying an existing population-based model that predicts tobacco use, radon exposure, and lung cancer mortality. The modified model will be used to elucidate the relative impact and cost-effectiveness of residential radon remediation strategies versus smoking reductions on radon-related lung cancer.

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 Krewski et al. (2005, 2006; North American studies) and Darby et al. (2005, 2006; European studies).