# 2. HEALTH EFFECTS

## 2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to radon. Its purpose is to present levels of significant exposure for radon based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of radon and (2) a depiction of significant exposure levels associated with various adverse health effects.

Radon is a relatively inert noble gas that does not readily interact chemically with other elements. However, radon is a radioactive element and evaluation of the adverse health effects due to exposure to radon requires a slightly different approach than other chemicals. 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-ray. 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 (See Appendix B for more information).

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 approximately 37 billion disintegrations (decay events) per second ($3.7 \times 10^{10}$ transformations per second). In discussing radon, a smaller unit, the picocurie (pCi) is used, where 1 pCi is equal to $1 \times 10^{-12}$ Ci. In international usage, the S.I. unit (the International System of Units) for activity is the Becquerel (Bq), which is equal to one disintegration per second or about 27 pCi. (Information for conversion between units is given in Chapter 9.) In the text of this profile, units expressed in pCi are followed by units in Bq contained in parentheses. The activity concentration of radon or another radionuclide in air is expressed in Ci/liter (L) of air ($Bq/m^3$). The activity concentration is a description of the exposure rather than the dose. In radiation biology 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 decays, it and its daughters (decay products) emit alpha and beta particles as well as gamma radiation. However, the health hazard from radon does not come primarily from radon itself, but rather from the radioactive products formed in the decay of radon. These products, called "radon daughters" or "radon progeny," are also radioactive (See Chapter 3 for more information on the chemical and physical properties of radon). Unlike

radon, the radon daughters are heavy metals and readily attach themselves to whatever they contact. The main health problems arise when radon daughters or dust particles carrying radon daughters are inhaled. Radon daughter particles attach to lung tissue and decay, resulting in the deposition of radiation (in the form of alpha particles) in the lung tissue.

Because it was not feasible to routinely measure the individual radon daughters, a unit termed the "Working Level" (WL) was introduced by the U.S. Public Health Service. The WL unit is a measure of the amount of alpha radiation emitted from the short-lived radon daughters (polonium-218, polonium-214, and lead-214) and represents any combination of short-lived radon progeny in one liter of air that will release $1.3 \times 10^5$ million electron volts (MeV) of alpha energy during decay. One WL is equivalent to $2.08 \times 10^5$ joules per cubic meter of air ($J/m^3$).

To convert between units of radon-222 radioactivity (Ci or Bq) and the potential alpha energy concentration (WL or $J/m^3$), the equilibrium between radon gas and radon daughters must be known (See Chapter 9 for conversion formula). When radon is in equilibrium with its progeny, that is, when each of the short-lived radon daughters is present at the same activity concentration in air as radon-222, then 1 WL equals 100 pCi radon-222/L of air. However, when removal processes other than radioactive decay are operative, such as with ventilation, the concentration of short-lived daughters will be less than the equilibrium amount. In such cases an equilibrium factor (F) is applied. For example, if the equilibrium factor is 0.5, then 200 pCi radon-222/L of air is equivalent to 1.0 WL; if the equilibrium factor is 0.3, then 1 WL corresponds to 333 pCi radon-222/L of air.

An additional unit of measurement used to describe human exposure to radon and radon progeny is the Working Level Month (WLM), which expresses both the intensity and duration of exposure. One WLM is defined as the exposure of a person to radon progeny at a concentration of 1.0 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 joule-hour per cubic meter of air ($J\text{-}h/m^3$); 1 WLM is equal to $3.6 \times 10^3$ $J\text{-}h/m^3$.

The WL and the WLM have been used to describe human exposure in occupational settings for uranium and other hard rock miners. Since the WLM represents both the intensity and duration of exposure, it alone does not provide enough information to determine the actual activity concentrations of radon in the air. For example, exposure to radon and radon daughters at 1 WL (100 pCi radon-222/L of air) for 100 working months (WM) results in a cumulative dose of 100 WLMs; exposure to 100 WL (10,000 pCi radon-222/L of air) for 1 WM also results in a cumulative dose of 100 WLMs

For both human and animal studies, exposures expressed in WLs were converted to pCi radon-222/L of air. The unit of activity, the curie (or Becquerel), is the appropriate unit to describe radon levels in the

environment, Unless otherwise stated by the authors of the studies reviewed, the equilibrium factors assumed for the conversion of WLs to pCi were 1.0 for animal studies and 0.5 for occupational epidemiological studies. For several of the epidemiological studies, exposure categories were expressed in WLMs without specific information concerning duration of radon exposure; therefore, for these studies dose conversions were not made. In this text and in the Supplemental Document, whenever possible radon levels are expressed in activity concentrations of pCi/L of air, pCi/kg of body weight, or pCi/L of water (along with the corresponding units in Becquerels).

Radon-222 is a direct decay product of radium-226, which is part of the decay series that begins with uranium-238 (see Chapter 3, Figure 3-l). Thorium-230 and thorium-234 are also part of this decay series. Uranium, thorium, and radium are the subject of other ATSDR Toxicological Profiles. Other isotopes of radon, such as radon-219 and radon-220, are formed in other radioactive decay series. However, radon-219 usually is not considered in the evaluation of radon-induced health effects because it is not abundant in the environment (Radon-219 is part of the decay chain of uranium-235, a relatively rare isotope) and has an extremely short half-life (4 seconds). Radon-220 is also usually not considered when evaluating radon-related health effects. While the average rate of production of radon-220 is about the same as radon-222, the amount of radon-220 entering the environment is much less than that of radon-222 because of the short half-life of radon-220 (56 seconds). All discussions of radon in the text refer to radon-222.

## 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual levels of exposure used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease

may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited.

### 2.2.1 Inhalation Exposure

Levels of significant exposure for the inhalation route for acute, intermediate, and chronic exposure duration (for which data exist) are presented in Table 2-l and illustrated in Figure 2-1.

#### 2.2.1.1 Death

No deaths in humans have been reported as the result of acute radon exposure. However, several epidemiological studies of individuals exposed over long periods have reported significant increases in early mortality due to cancer and nonneoplastic (noncancer) diseases (see Section 2.2.1.8 for a discussion on cancer). Descriptions of cancer mortality were presented by exposure categories, i.e., WLM categories; however, deaths due to noncancer respiratory effects were generally reported for the total cohort. Increased mortality as a result of nonneoplastic respiratory diseases, such as emphysema and pulmonary fibrosis, has been reported in United States uranium miners exposed to radon and radon daughters at concentrations in the range of 100 to 10,000 pCi radon-222/L of air (3,700 to 370,000 Bq/$m^3$) (Lundin et al. 1971; Waxweiler et al. 1981). The concentration of radon and radon daughters in mine air was reported to result in cumulative exposures of from 50 WLM to levels equal to or greater than 3,720 WLM. The incidence of mortality from respiratory diseases other than cancer and tuberculosis has been reported for uranium miners and related to cumulative exposure expressed in WLMs (Archer et al. 1976). As exposure increased, the number of cases per 1,000 individuals exposed also increased. However, there are a number of confounding factors to consider in all of these studies, including exposure to other agents, ethnicity, smoking history, and work experience. The cases of nonneoplastic respiratory diseases reported in these miners cannot be attributed solely to radon or radon daughters but may be due to exposure to silica, to other mine pollutants, to smoking, or to other causes.

In a more recent study (Roscoe et al. 1989) mortality from nonmalignant respiratory disease was reported for a cohort of white nonsmoking uranium miners. Deaths from these diseases were twelve times higher in uranium miners than in nonsmoking United States veterans. Causes of death in the cohort included silicosis, chronic obstructive pulmonary disease, fibrosis, and emphysema. However, the exposure history of the individuals having these

**TABLE 2-1. Levels of Significant Exposure to Radon - Inhalation**

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (pCi/L) | LOAEL (Effect) Less Serious (pCi/L) | LOAEL (Effect) Serious (pCi/L) | Reference |
|---|---|---|---|---|---|---|---|
| ACUTE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 1 | Mouse | 1d<br>5-40hr | | | | $2.2x10^8$ (30 day LD50)[a] | Morken 1955 |
| Systemic | | | | | | | |
| 2 | Mouse | 1d<br>5-40hr | Hemato | | | $2.2x10^8$ (anemia) | Morken 1955 |
| INTERMEDIATE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 3 | Rat | 4-6mo<br>2d/wk<br>1hr/d | | $3.0x10^3$ | | | Chameaud et al. 1984 |
| 4 | Rat | lifespan<br>2d/wk<br>90hr/wk | | | | $4.8x10^6$ (dec lifespan) | Palmer et al. 1973 |
| 5 | Mouse | lifespan<br>150hr/wk | | | | $4.2x10^5$ (dec lifespan) | Morken and Scott 1966 |
| 6 | Hamster | lifespan<br>2d/wk<br>90hr/wk | | | | $4.8x10^6$ (dec lifespan) | Palmer et al. 1973 |
| Systemic | | | | | | | |
| 7 | Rat | lifespan<br>2d/wk<br>90hr/wk | Resp<br>Other | | $4.8x10^6$ (dec bw) | $4.8x10^6$ (metaplasia)[b] | Palmer et al. 1973 |
| 8 | Mouse | lifespan<br>150hr/wk | Resp<br>Hemato<br>Other | | $4.2x10^5$ (dec lymphocytes)<br>$4.2x10^5$ (dec bw) | $4.2x10^5$ (metaplasia) | Morken and Scott 1966 |

**TABLE 2-1 (Continued)**

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (pCi/L) | LOAEL (Effect) Less Serious (pCi/L) | LOAEL (Effect) Serious (pCi/L) | Reference |
|---|---|---|---|---|---|---|---|
| 9 | Mouse | lifespan<br>2d/wk<br>90hr/wk | Resp<br>Other | | $4.8x10^6$ (dec bw) | $4.8x10^6$ (fibrosis) | Palmer et al. 1973 |
| 10 | Hamster | lifespan<br>2d/wk<br>90hr/wk | Resp<br>Other | | $4.8x10^6$ (dec bw) | $4.8x10^6$ (metaplasia) | Palmer et al. 1973 |
| 11 | Dog | 1-50d<br>5d/wk<br>20hr/d | Resp | | | $5.5x10^5$ (fibrosis)[c] | Morken 1973 |
| Cancer | | | | | | | |
| 12 | Rat | 2.5-8wk<br>4d/wk<br>3-6hr/d | | | | $3.0x10^5$ (CEL-lung) | Chameaud et al. 1982 |
| 13 | Rat | 25-115 d<br>4-5hr/d | | | | $7.5x10^5$ (CEL-lung) | Chameaud et al. 1974 |
| 14 | Rat | 4-6mo<br>2d/wk<br>1hr/d | | | | $3.0x10^3$ (CEL-lung) | Chameaud et al. 1984 |
| CHRONIC EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 15 | Hamster | lifespan<br>5d/wk<br>6hr/d | | $3.1x10^5$ | | | Pacific Northwest Laboratory 1978 |
| Systemic | | | | | | | |
| 16 | Human | >1mo-18yr<br>(occup) | Resp | | | >$1.0x10^2$ (tuberculosis) | Waxweiler et al. 1981 |
| 17 | Hamster | lifespan<br>5d/wk<br>6hr/d | Resp<br>Hemato<br>Other | $3.1x10^5$ | $2.6x10^5$ (dec bw) | $2.6x10^5$ (hyperplasia)[d] | Pacific Northwest Laboratory 1978 |

**TABLE 2-1 (Continued)**

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (pCi/L) | LOAEL (Effect) Less Serious (pCi/L) | LOAEL (Effect) Serious (pCi/L) | Reference |
|---|---|---|---|---|---|---|---|
| Cancer | | | | | | | |
| 18 | Human | 0.5-23yr (occup) | | | | $3.4x10^2$ (CEL-lung) | Gottlieb and Husen 1982 |
| 19 | Human | (occup) | | | | $2.0x10^2$ (CEL-lung) | Morrison et al. 1981 |
| 20 | Human | 0-14yr (occup) | | | | $1.0x10^2$ (CEL-lung)[e] | Solli et al. 1985 |
| 21 | Human | >29yr (occup) | | | | $6.0x10^1$ (CEL-lung) | Edling and Axelson 1983 |
| 22 | Human | >1yr->20yr (occup) | | | | $5.0x10^1$ (CEL-lung) | Damber and Larsson 1985 |
| 23 | Human | 48wk/yr 48hr/wk (occup) | | | | $5.0x10^1$ (CEL-lung) | Howe et al. 1987 |
| 24 | Human | >10yr (occup) | | | | $>3.0x10^1$ (CEL-lung) | Snihs 1974 |
| 25 | Human | >2-30yr (res) | | | | $1.5x10^0$ (CEL-lung) | Svensson et al. 1987 |
| 26 | Human | (occup) | | | | $2.4x10^2$ (CEL-lung) | Fox et al. 1981 |
| 27 | Human | >1mo-18yr (occup) | | | | $1.0x10^2$ (CEL-lung) | Waxweiler et al. 1981 |
| 28 | Human | >1mo-30yr (occup) | | | | $4.0x10^2$ (CEL-lung) | Roscoe et al. 1989 |

[a] $2.2x10^8$ presented in Table 1-2.
[b] $4.8x10^6$ presented in Table 1-2.
[c] $5.5x10^5$ presented in Table 1-2.
[d] $2.6x10^5$ presented in Table 1-2.
[e] 100 presented in Table 1-1.

NOAEL=no-observed-adverse-effect level; LOAEL=lowest-observed-adverse-effect level; pCi/L=picocurie per liter; d=day; hr=hour; wk=week; mo=month; CEL=Cancer Effect Level; yr=year; hemato=hematological; resp=respiratory; occup=occupational; dec=decreased; bw=body weight; res=residential

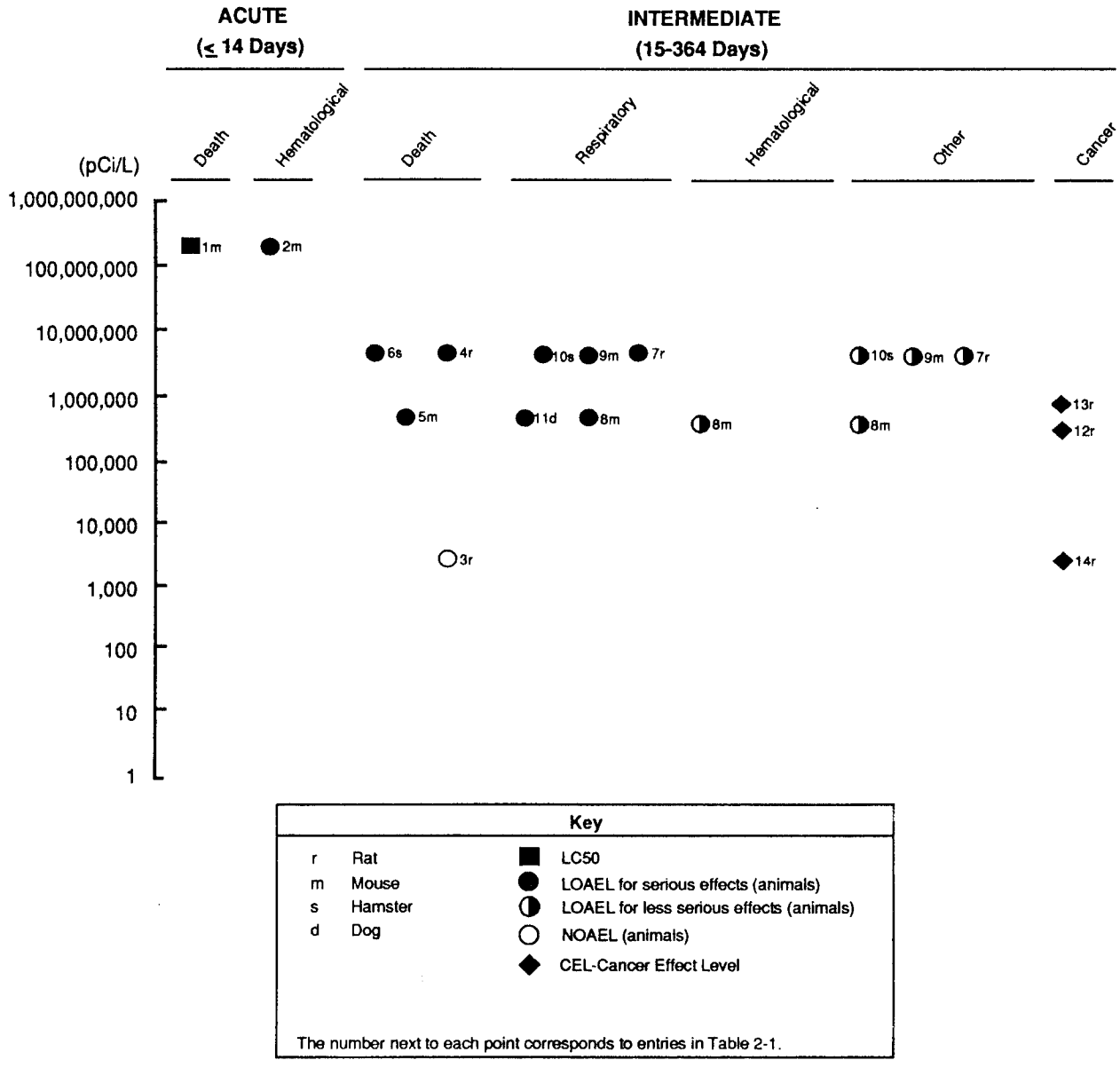


**FIGURE 2-1. Levels of Significant Exposure to Radon - Inhalation**

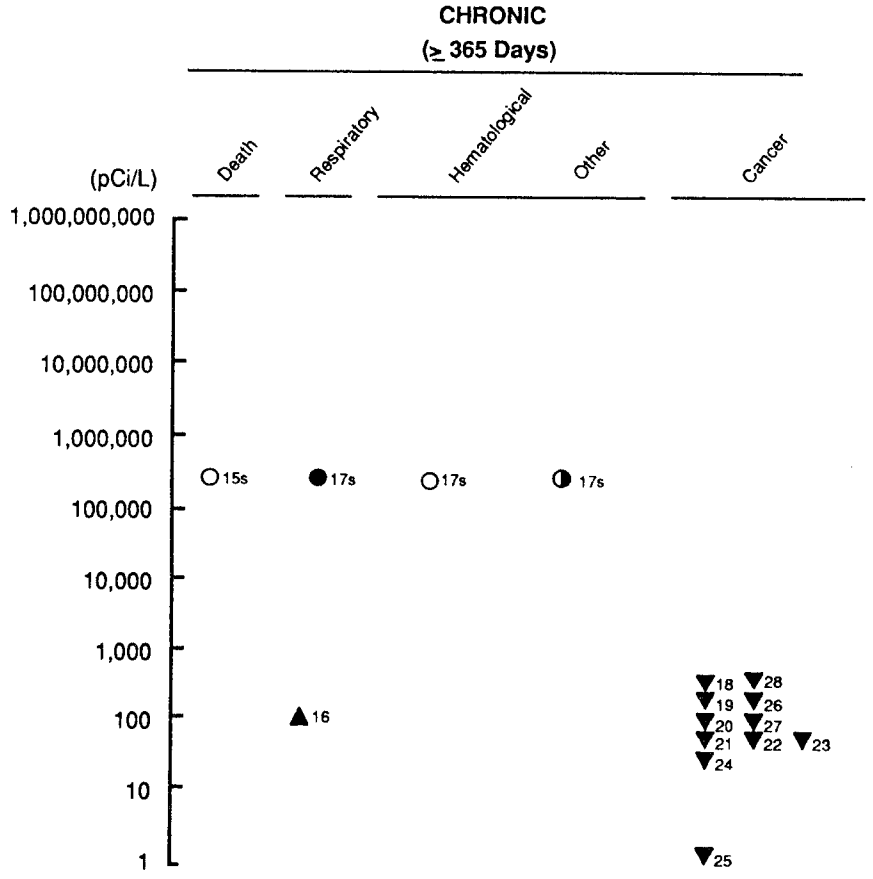


**FIGURE 2-1 (Continued)**

diseases was not reported. Excepting cigarette smoking, this study has all of the confounding factors mentioned previously.

Mortality due to nonneoplastic respiratory diseases was not significantly elevated in other uranium mining cohorts including miners in Czechoslovakia (Sevc et al. 1988) or Ontario, Canada (Muller et al. 1985). Although environmental radon levels were not reported in either the Czechoslovakian or Canadian studies, cumulative occupational exposure to radon and radon daughters were estimated at levels up to about 600 WLMs. A statistically significant excess of mortality due to chronic nephritis and renal sclerosis was also reported in the United States 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).

The acute lethal effects of radon and radon daughters have been studied in mice. A 30-day $LD_{50}$ was estimated based on single exposures via inhalation to radon and radon daughters at a concentration of $2.2 \times 10^8$ pCi/L ($8.1 \times 10^9$ Bq/$m^3$)for 5 to 40 hours (Morken 1955). After 40 hours of exposure, 100% of the exposed mice died within 2 weeks (cause of death was not reported), while no deaths occurred within 60 days following an exposure of 26 hours or less.

Significant decreases in the lifespan of laboratory animals exposed to high doses of radon and radon daughters were reported by several investigators (Cross 1987; Morken 1973; Morken and Scott 1966; Palmer et al. 1973). Respiratory system insult contributed to the death of treated animals in these studies, although the actual cause of death was not reported. The lifespan of male and female mice (median lifespan of controls was 79 and 98 weeks) was reduced by 55% and 42%, respectively, as a result of continuous exposure (150 hours/week) to $4.2 \times 10^5$ pCi radon-222/L of air ($1.6 \times 10^7$ Bq/$m^3$) for up to 47 weeks (Morken and Scott 1966). Emaciation, reddening of the ears, and abnormal grooming was observed preceding death. Pseudoparalysis was observed in mice which died a few days after exposure (Morken and Scott 1966). A similar decrease in lifespan was observed in rats and hamsters following exposure to $4.8 \times 10^6$ pCi radon-222/L of air ($1.8 \times 10^8$ Bq/$m^3$) for 90 hours/week (Palmer et al. 1973). All animals in the Palmer et al. (1973) study died by the fourth month of treatment, while all treated animals in the Morken and Scott (1966) study died by the eleventh month. At lower concentrations (3,000 pCi radon-222/L of air [$1.1 \times 10^5$ Bq/$m^3$] for 2 hours/week, 6 months) the lifespan of rats was not decreased (Chameaud et al. 1984).

#### 2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, dermal, or ocular effects in humans or animals after inhalation exposure to radon and radon daughters.

**Respiratory Effects**. Adverse respiratory effects have been observed in humans under occupational conditions and in laboratory animals exposed to

radon and radon daughters. Epidemiology studies of miner cohorts report an increased frequency of chronic, nonneoplastic lung diseases, such as emphysema and pulmonary fibrosis, among uranium miners in the United States (Lundin et al. 1971; Roscoe et al. 1989; Waxweiler et al. 1981) and among Cornish tin miners (Fox et al. 1981), and chronic interstitial pneumonia among Canadian uranium miners (Muller et al. 1985). 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 repiratory disease compared to a nonsmoking United States veteran cohort (Roscoe et al. 1989).

Alterations in respiratory function in United States uranium miners have been reported (Archer et al. 1964; Samet et al. 1984a; Trapp et al. 1970). Analyses among United States uranium miners indicated a loss of 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. The individual contributions of these factors to the observed adverse respiratory effects are not defined.

No studies were located regarding the respiratory effects of radon and radon daughters in laboratory animals following acute exposure. Respiratory toxicity occurred in mice, hamsters, dogs, and rats following exposure to radon and radon daughters for intermediate exposure durations. Chronic inflammation (radiation-induced pneumonitis), pneumonia, and/or fibrosis of varying degrees in the alveolar region occurred in most animals exposed to radon and radon daughters ($4.2 \times 10^5$ to $4.8 \times 10^6$ pCi radon-222/L of air [$1.6 \times 10^7$ to $1.8 \times 10^8$ Bq/$m^3$]) for 4 to 150 hours/week for 10 to approximately 45 weeks (Chaumeaud et al. 1974; Morken 1973; Morken and Scott 1966; Palmer et al. 1973). In these studies, the relationship of dose, temporal dosing pattern, and length of exposure to onset of effects is unclear since the time of onset of effects was rarely reported or effects were reported only when animals died or were sacrificed.

In Palmer et al. (1973), rats, mice, and hamsters, were exposed to radon [$4.8 \times 10^8$ pCi radon/L of air ($1.8 \times 10^5$ Bq/$m^3$)] via inhalation for approximately 90 hours per week, in two continuous 45-hour periods. These animals were allowed to die, or were sacrificed when moribund, after which they were histopathologically examined. At four months of exposure, only one of the rodents remained alive. The radiation effects observed in these animals, which included interstitial pneumonitis or septal fibrosis, were found at post-mortem examination. Therefore the onset of respiratory effects could not be determined.

In a study conducted by Morken and Scott (1966), mice were to be exposed to $4.2 \times 10^5$ pCi radon/L of air ($1.6 \times 10^7$ Bq/$m^3$) 150 hours/week for life. However, by week 15 of the experiment the median lifetime of the animals had been decreased by 50%. However, the cause of this decreased lifespan -was not

reported. The authors then sacrificed the remaining animals (15 treated mice and 3 control mice) for purposes of histopathological examination. Tracheal effects, including thickening of the mucous membrane, inflammation of the mucous glands, and destruction of cells lining the trachea, were observed. However, the onset of these effects could not be determined. In Morken (1973) 9 mice and dogs were exposed to radon for intermediate periods of time and then sacrificed at designated times post-exposure. In mice exposed to $5.5x10^5$ pCi radon/L of air ($2.0x10^7$ Bq/$m^3$) for 10, 15, 20, or 25 weeks, lesions of the trachea and bronchi were observed immediately post-exposure, but by eight weeks post-exposure tissues appeared normal. However, with increasing time post-exposure, the epithelial lining of the terminal bronchiole became flattened or disappeared. At long intervals after exposure to radon for 25 weeks, non-specific pulmonary effects, including small foci of interstitial fibrosis, were observed in mice. In dogs exposed to radon for one to 50 days [$5.5x10^5$ pCi of radon/L of air ($2.0x10^7$ Bq/$m^3$)], no significant effects were observed in treated dogs immediately post-exposure compared to untreated controls. At one and two years post-exposure, there was a "probable increasing relation" to dose of small foci of chronic inflammation. At three years post-exposure, this relation had disappeared in dogs exposed to low doses of radon up to 800 WLM, but was still considered "probable" for the larger doses. However, a definite time of onset of respiratory effects in either mice or dogs could not be determined from the results of this study.

Respiratory effects similar to those observed following intermediate exposure have also been observed in laboratory animals following chronic exposure to radon and radon daughters. Respiratory lesions, mainly squamous metaplasia, were observed in the bronchioalveolar region of hamsters 8 months following initiation of lifetime exposure to $2.6x10^5$ pCi radon-222/L of air ($9.6x10^6$ Bq/$m^3$) for 30 hours/week (Pacific Northwest Laboratory 1978).

Pulmonary fibrosis in rats, hamsters, and dogs and emphysema in hamsters and dogs occurred following exposure to radon and radon daughters and uranium ore dust (Cross et al. 1984, 1985, 1986; Pacific Northwest Laboratory 1978). In hamsters emphysema was produced as a result of exposure to uranium ore alone, diesel exhaust alone, and radon and radon daughters alone; however, emphysema was not observed in hamsters at cumulative doses of radon of less than 7,000 WLM (Pacific Northwest Laboratory 1978). Fibrosis occurred in hamsters following exposure to radon and radon daughters at a cumulative dose of 8,000 WlM in combination with uranium ore and diesel exhaust, but not with radon and radon daughters alone at cumulative exposure at approximately 7,000 WLM. However, the incidence of bronchial hyperplasia was significantly greater in hamsters receiving radon and radon daughters alone. In dogs the combination of uranium ore dust and radon and radon daughters produced more severe emphysema and fibrosis than uranium ore dust alone; however, radon and radon daughters alone were not tested in dogs (Pacific Northwest Laboratory 1978). Fibrosis, but not emphysema, was observed in rats exposed to radon and radon daughters and uranium ore dust (Cross et al. 1984, 1985). These studies are discussed further in Section 2.6.

**Renal Effects.** A statistically significant increase in mortality due to kidney disease, characterized by chronic nephritis and renal sclerosis, was reported among United States uranium miners (Waxweiler et al. 1981) and in Canadian miners at the Eldorado mines (Muller et al. 1985). Kidney toxicity has been induced experimentally in animals exposed to uranium (ATSDR 1990a). Kidney disease was not reported among other mining cohorts and no studies were located regarding renal effects in laboratory animals following inhalation exposure to radon. It is not clear whether the kidney effects observed by Waxweiler were due to radon, uranium ore, or other mining and nonmining factors.

**Hematological Effects.** No studies were located regarding hematological effects in humans after inhalation exposure to radon.

Hematological effects have been observed in mice following acute and chronic exposure to radon and radon daughters. The extent and severity of the hematological effects in mice were exposure related. Effects following acute exposure, either a single or multiple exposures, were transient. Recovery to control values occurred within a shorter time post-exposure after a single acute exposure than with multiple exposures. Chronic exposure of mice to radon-222 resulted in dose-related alterations to the hematological system.

Following a single exposure to mice of $1.76 \times 10^{8}$ pCi radon-222/L of air ($6.5 \times 10^{9}$ Bq/m$^3$), transient decreases in erythrocytes, reticulocytes, platelets, and white blood cells were observed immediately post-exposure (Morken 1961). Platelets and white blood cells returned to control levels by 50 days post-exposure, and reticulocytes increased 50% to 100% over controls within 2 to 3 weeks, but returned to normal about one year after exposure. Erythrocyte counts remained depressed for one-year post-exposure (Morken 1961). In mice exposed 2 or 4 times at concentrations of $2.11 \times 10^{8}$ pCi radon-222/L of air ($7.8 \times 10^{9}$ Bq/m$^3$), erythrocyte counts remained depressed compared to controls, while platelets and neutrophils rapidly decreased and then recovered within 2 weeks (Morken 1964). After multiple exposures, lymphocyte counts remained lower for longer periods of time compared to single exposures, indicating that recovery was affected by larger or repeated doses (Morken 1964). These effects are based on results observed in small numbers of animals.

In mice, lifetime exposure to $4.2 \times 10^{5}$ pCi radon-222/L of air ($1.6 \times 10^{7}$ Bq/m$^3$) , 150 hours/week resulted in mild, progressive anemia in male mice and a decrease in lymphocyte count in male and female mice, which was linearly related to cumulative dose as expressed in working level months (WLMs) (Morken and Scott 1966). However, no hematological effects were observed in hamsters exposed to $3.1 \times 10^{5}$ pCi radon-222/L of air ($1.1 \times 10^{7}$ Bq/m$^3$) (Pacific Northwest Laboratory 1978).

**Other Systemic Effects.** Exposure to radon and radon daughters at concentrations ranging from $2.6 \times 10^{5}$ to $4.8 \times 10^{6}$ pCi radon-222/L of air ($9.6 \times 10^{6}$

to $1.8 \times 10^{8}$ Bq/$m^3$), 30 to 150 hours/week, resulted in a significant decrease in body weight in hamsters (Pacific Northwest Laboratory 1978), mice (Morken and Scott 1966; Palmer et al. 1973), and rats (Palmer et al. 1973). There was no explanation given for these weight losses and food consumption was not reported in any of the studies.

#### 2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans and animals after inhalation exposure to radon.

#### 2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to radon. Two guinea pigs exposed to approximately $4.7 \times 10^{10}$ to $5.8 \times 10^{10}$ pCi ($1.7 \times 10^{9}$ to $2.15 \times 10^{9}$ Bq) radon for 1 to 2% hours became drowsy, their respiration increased, and after several hours, they died (Proescher 1913). Autopsy showed that both animals died from respiratory paralysis caused by central nervous system failure. The study has many limitations, such as the use of only two animals and the possibility that oxygen deprivation contributed to the respiratory failure. A causal relationship between central nervous system failure and radon exposure was not established.

#### 2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans and animals after inhalation exposure to radon.

### 2.2.1. Reproductive Effects

No maternal or fetal reproductive effects in humans have been attributed to exposure to radon and radon daughters. 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 radon daughters (Dean 1981; Muller et al. 1967; Wiese and Skipper 1986). The secondary sex ratio of the first born children of uranium miners was decreased with cumulative exposure to radon and radon daughters in miners whose median age at the time of conception was less than 25 years of age but was increased with cumulative exposure to radon and radon daughters in miners whose median age at the time of conception was greater than 25 years of age (Waxweiler and Roscoe 1981). This age effect was also observed when the miners were analyzed according to race.

No studies were located regarding reproductive effects in animals following inhalation exposure to radon and radon daughters.

### 2.2.1.7 Genotoxic Effects

Some epidemiologic studies have indicated that radon and radon daughters may produce genotoxic effects in persons exposed in occupational and environmental settings. Brandom et al. (1978) reported a higher incidence of chromosomal aberrations among uranium miners exposed to radon and radon daughters at cumulative exposures ranging from <100 to >3,000 WLM, as compared to their matched controls. A clear exposure-related increase was observed for the groups exposed to 770 to 2,890 WLM with a sharp decrease at the highest dose group (>3,000 WLM). The cause of the reversal in exposure-response at the highest dose is unclear, Increases in chromosomal aberrations were also 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-Rfiling and Fischer 1979, 1982; Pohl-Rtiling 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 [$1.1 \times 10^5$ Bq/$m^3$]). The study further indicated higher DNA-repair rates in juvenile cells than in fully differentiated cells.

Evidence of chromosomal aberrations was equivocal in an animal study. Rabbits exposed to high natural background levels of radon-222 (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 post-exposure (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).

### 2.2.1.8 Cancer

Significant excesses in deaths from lung cancer have been identified in epidemiology studies of uranium miners and other hard rock miners. Statistically significant excesses in lung cancer deaths have been reported in uranium miners in the United States (Archer et al. 1973, 1976, 1979; Gottlieb and Husen 1982; Hornung and Meinhardt 1987; Lundin et al. 1971; Roscoe et al. 1989; Samet et al. 1984b, 1989; Wagoner et al. 1964; Waxweiler et al. 1981), Czechoslovakia (Sevc et al. 1988), and Canada (Howe et al. 1986, 1987; Muller et al. 1985).

The results of these studies are consistent and demonstrate that the frequency of respiratory cancer mortality increased with increasing exposure to radiation (cumulative WLMs). Statistically significant excesses in lung cancer deaths were present after cumulative exposures of less than 50 WLMs in the Czechoslovakian cohort (Sevc et al. 1988) and at cumulative exposures greater than 100 WLMs in the cohorts from the United States and Ontario, Canada (Muller et al. 1985; Samet et al. 1989; Waxweiler et al. 1981). These studies indicate that lung cancer mortality was influenced by the total cumulative radiation exposure, by the age at first exposure, and by the timecourse of the exposure accumulation. Most deaths from respiratory cancers occurred 10 or more years after the individual began uranium mining (Lundin et al. 1971). Among uranium miners, epidermoid, small cell undifferentiated, and adenocarcinoma were present with increased frequency, while large-cell undifferentiated and other morphological types of lung cancer were seen less frequently (Archer et al. 1974).

The evidence for radon daughter-induced lung cancer is further supported by epidemiological studies conducted among nonuranium hard rock miners. The lung cancer mortality rate was also statistically higher in iron ore miners in Sweden (Damber and Larsson 1982; Edling and Axelson 1983; Jorgensen 1984; Radford and Renard 1984; Snihs 1974); metal miners in the United States (Wagoner et al. 1963); zinc-lead miners in Sweden (Axelson and Sundell 1978); tin miners in England (Fox et al. 1981); phosphate miners in Florida (Checkoway et al. 1985; Stayner et al. 1985); in a niobium mine (Solli et al. 1985); and Newfoundland fluorspar miners (Morrison et al. 1985). In some of these mines, the main source of radon and radon daughters was from radon dissolved in groundwater. Based on measurements of radon concentrations in mine air, significant excesses in lung cancer mortality were reported at concentrations of 30 pCi radon-222/L of mine air (111 $Bq/m^3$) and greater (Snihs et al. 1974). Since exposure was for at least 10 years, the cumulative exposure to workers was approximately 36 WLMs or greater. This excess cancer mortality occurred at cumulative exposures as low as 5 WLMs (Howe et al. 1987) but generally at cumulative doses greater than 100 WLMs.

In a subcohort of 516 white nonsmoking uranium miners (drawn from a larger cohort of United States 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 United States veterans. No lung cancer deaths were found in nonsmoking miners who had exposure less than 465 WLMs (Roscoe et al. 1989). Unlike the nonmining cohort, the miners in the subcohort may have been exposed to other mining pollutants, e.g., diesel exhaust and silica dusts. The contribution of these factors was not considered in the analysis.

Several case-control studies have examined the association between lung cancer and housing construction materials, or between lung cancer and residential radon exposure. The majority of these have been conducted in Sweden (Axelson and Edling 1980, Axelson et al. 1979, 1981; Edling 1984; Svensson 1987, 1989). The Axelson studies examined the association between

housing type and lung cancer risk. Residences of cases (having died from lung cancer) and controls (having died from noncancer causes) were classified into three categories: having lived in wooden house without basements; brick, concrete, or granite houses with basements; and a mixed category (all other types of houses). No radon measurements were taken in these homes. However, previous studies in Sweden had shown that, in general, the wooden structures had lower radon levels than brick or concrete structures. Axelson reported a statistically significant trend for increased lung cancer deaths associated with residence in mixed category houses or in stone houses with basements (Axelson and Edling 1980, Axelson et al. 1979). These studies were adjusted for age and sex, but not for smoking history. An additional study based on the same approach (lung cancer associated with type of residence) did measure radon levels in residences of interest (Edling et al. 1984). Wooden houses without basements had mean levels of 1.1 pCi/L (42 Bq/$m^3$), wooden houses with a basement on radiation producing ground or plaster houses had mean levels of 4.6 pCi/L (170 Bq/$m^3$), while all other types of houses had mean levels of 1.5 pCi/L (57 Bq/$m^3$). Again, the association of incidence of lung cancer, adjusted for age and sex, and additionally for smoking, with type of residence and with radon levels, showed a significantly increasing trend (Axelson et al. 1981, Edling et al. 1984). All of the above studies have one or more methodological limitations, such as small cohort size and limited or no measurement of radon levels in homes.

Another study of a Swedish cohort has also reported significant correlation between incidence of lung cancer, type of residence, and radon exposure, although only 10% of residences were monitored for radon. In addition, it correlates levels of exposure with particular types of lung cancer. Association of exposure with lung cancer, adjusted for smoking, age, and degree of urbanization, was strongest for small cell carcinoma of the lung (Svensson et al. 1989). This particular type of lung tumor has also been reported in cohorts of United States uranium miners.

A study of lung cancer in adult white residents in Maryland reported an association of lung cancer with age, sex, and smoking. Lung cancer rates were highest in houses which had concrete walls and in houses without basements but with concrete slabs, but this association was very slight (Simpson and Comstock 1983).

Identification of specific cancer effect levels, i.e., the environmental concentration of radon and radon daughters, was not feasible for all of the epidemiological studies because of the quality of the exposure information provided. Environmental levels of radon and radon daughters, expressed in pCi radon-222/L of air, present in mines were measured at various times; however, actual measurements of radon and radon daughter levels were not available for every mine and for every year of exposure. Rather, actual measurements along with estimates of radon daughter levels based on extrapolations from actual measurements were then combined with individual work histories to derive estimates of cumulative radon daughter exposure for each individual, reported in WLMs. Workers were then classified into cumulative WLM exposure

categories. For example, in the United States uranium mining cohort radon and radon daughter levels in mines were measured from 1950 to 1968 and ranged from >100 to >10,000 pCi radon-222/L of air (>$3.7 \times 10^3$ to >$3.7 \times 10^5$ Bq/$m^3$) (>0.5 to >50 WLs) across various mines and years. Miners were employed in the mines for 4 to 28 years with an average length of employment of 15 years (Saccomanno et al. 1988). The resulting exposure categories ranged from >120 WLM to ≥3,720 WLMs. Only a few of the epidemiological studies provided enough exposure information to express exposures in pCi radon-222/L of air. However, the quality of the exposure measurements does not alter the conclusion that, based on the epidemiology studies, exposures to radon and radon daughters at cumulative doses greater than 100 WLMs resulted in excesses in lung cancer mortality, with the exception of the nonsmoking cohort reported by Roscoe et al. (1989), which reported excesses in lung cancer at higher doses.

No studies were located regarding cancer in laboratory animals following acute exposure to radon and radon daughters. Lung tumors have been observed in rats following intermediate exposure at concentrations as low as 3,000 pCi radon-222/L of air ($1.1 \times 10^5$ Bq/$m^3$) 2 hours/week for 4 months (Chameaud et al. 1984) and up to $3 \times 10^6$ pCi radon-222/L of air ($1.1 \times 10^8$ Bq/$m^3$) 12 hours/week for 2 weeks (Chameaud et al. 1974, 1982a, 1982b). The mean time to death with tumor in the Chameaud et al. (1984) study was approximately 112 weeks, which is close to the normal lifespan for a rat (104 weeks). In Chameaud et al. (1980)s lung cancers were not observed in rats until the 24th month of the study. These studies would indicate that the latency period for radon-induced lung tumors is long. No treatment-related cancers were observed in dogs, mice, or rats following exposure to radon and radon progeny alone [5.5x105 to $1 \times 10^6$ pCi radon-222/L of air ($2.0 \times 10^7$ to $3.7 \times 10^7$ Bq/$m^3$)], 25 to 150 hours/week (Morken 1973). In this study, dogs were exposed for 1 to 50 days, mice (three separate experiments) for 8 weeks to life, and rats for 24 weeks. However, the dog study was terminated at 3 years; the rat study only reported results through the twelfth month of the study; and two of the mouse studies had lifespan shortening. Some of the changes observed may have been preneoplastic. However, based on the results from the Chameaud et al. (1980, 1984) studies, lifespan shortening or the early termination of experiments may have precluded the development of tumors. In the remaining mouse study reported by Morken (1973), mice were sacrificed beginning at 60 weeks of age, following exposure to radon for 10, 15, 20, or 25 weeks, at 10 week intervals until all of the mice were killed (110 weeks). No treatment-related cancers were reported. However, reviewers of this study (Cross 1987) report that laboratory room air containing dusts and oil and water droplets may be a confounding factor in this study. The influence of these confounding factors is uncertain, but may have led to a more rapid solubilization of radon progeny causing a decrease in observed lung effects.

In other studies in which a significant increase in the incidence of lung cancer was not reported, the respiratory lesions that were observed following exposure to radon and radon daughters alone were considered by the authors to be "precancerous" (Morken and Scott 1966; Pacific Northwest Laboratory 1978; Palmer et al. 1973). In the Morken and Scott (1966) study, destructive

hyperplastic and metaplastic lesions were observed in the trachea and bronchioles of mice following exposure to $4.2x10^5$ pCi radon-222/L of air ($1.6x10^7$ Bq/$m^3$) 150 hours/week for life, but no carcinomas were observed. However, there was a significant shortening of lifespan in the study, with many of the animals dead at 35 weeks of age. Because of this lifespan shortening, the animals may not have lived long enough to develop tumors. In a study reported by Palmer et al. (1973), no treatment-related cancers were observed in mice, rats, or hamsters exposed to $4.8x10^6$ pCi radon-222/L of air ($1.8x10^8$ Bq/$m^3$), but precancerous respiratory effects were observed in mice and rats, such as hyperplasia. The lack of cancer may be attributed to the fact that all of the animals but one were dead by the fourth month of the study. However, the cause of death was not reported. In a separate study, "precancerous" respiratory effects (fibrosis) were observed in dogs exposed to $1.1x10^5$ pCi radon-222/L of air ($4.1x10^6$ Bq/$m^3$) (Pacific Northwest Laboratory 1978). The lack of cancer observed in dogs may be due to lifespan shortening (4 years in treated versus 7 years in the normal dog), although the lifespan of untreated controls in this study was comparable.

Following chronic exposure to radon and radon daughters alone, no statistically significant increase in the incidence of any type of tumor was observed in hamsters exposed to $3.1x10^5$ pCi radon-222/L of air ($1.1x10^7$ Wm3> , 30 hours/week for life, although pulmonary fibrosis and bronchial hyperplasia were observed (Pacific Northwest Laboratory 1978). Hamsters may be resistent to alpha radiation-induced lung cancer since no lung tumors were produced in hamsters exposed to another alpha-emitter, plutonium (ATSDR 1990b).

Lung cancer was reported in laboratory animals by Chameaud et al. (1974), Cross et al. (1982a, 1982b, 1984), and Stuart et al. (1970) following chronic administration of radon and radon daughters in conjunction with air pollutants, such as cigarette smoke, uranium ore dusts, or diesel exhaust (see Section 2.6).

### 2.2.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to radon and radon daughters.

**2.2.2.1 Death**
**2.2.2.2 Systemic Effects**
**2.2.2.3 Immunological Effects**
**2.2.2.4 Neurological Effects**
**2.2.2.5 Developmental Effects**
**2.2.2.6 Reproductive Effects**

**2.2.2.7 Genotoxic Effects**

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 $2.9x10^4$ to $1.2x10^6$ pCi radon-222/L of water ($1.1x10^3$ to $4.4x10^4$ 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.

**2.2.2.8 Cancer**

Limited information was located regarding cancer in humans after exposure to radon and radon daughters in water. 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. The authors note that correlation does not demonstrate causation and that confounding factors (e.g., smoking) exist. In addition, exposure from radon in these water supplies could have been by the inhalation route as well as the oral route.

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

**2.2.3 Dermal Exposure**

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

**2.2.3.1 Death**
**2.2.3.2 Systemic Effects**
**2.2.3.3 Immunological Effects**
**2.2.3.4 Neurological Effects**
**2.2.3.5 Developmental Effects**
**2.2.3.6 Reproductive Effects**
**2.2.3.7 Genotoxic Effects**

**2.2.3.8 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-222/$cm^2$ skin surface area (Sevcova et al. 1978). The authors believe that the causal agent may be exposure to radon and radon daughters. However, they acknowledge that exposure to other agents in the uranium mining environment, as well as minor traumas of the skin, may also play a role in the 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.

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

### 2.2.4 Other Routes of Exposure

#### 2.2.4.1 Death

A single intravenous injection of $1.6 \times 10^{10}$ pCi ($6.0 \times 10^{8}$ Bq) radon-222/kg body weight in equilibrium with its decay products resulted in a 56% decrease in the average lifespan of mice (Hollcroft et al. 1955). This decrease was believed to be due to radiation-induced renal failure as indicated by inflammatory lesions and atrophy of the renal cortex as seen in most of the radon treated animals. The study by Hollcroft et al. (1955) has methodological deficiencies including an erratic schedule for sacrifice of animals and the failure to examine animals that died from acute radiation injury. Many other causes of such renal effects are known and the relevance of these effects is questionable following near lethal doses of radon.

#### 2.2.4.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, or dermal/ocular effects in humans or animals after exposure to radon and radon daughters by other routes of exposure.

**Hematological Effects.** No studies were located regarding hematological effects in humans after exposure to radon and radon daughters by other routes.

A single intravenous injection of $1.6 \times 10^{8}$ pCi ($6.0 \times 10^{8}$ Bq) radon-222/kg body weight in equilibrium with its decay products in mice resulted in a decrease in red blood cell count within 2 weeks, which remained depressed until death of the mice at about 150 to 180 days (Hollcroft et al. 1955). The anemia observed was associated with the observed renal failure in these animals. White blood cell counts were decreased immediately post-exposure, but soon returned to normal levels. (See Section 2.2.4.1 for limitations of Hollcroft et al. 1955.)

**Renal Effects.** No studies were located regarding renal effects in humans after exposure to radon and radon daughters by other routes.

A decrease in kidney weight, extreme shrinkage of the cortex, and infiltration of fat into the lining of the renal tubules and eventual renal failure occurred in mice given a single intravenous injection of $1.6 \times 10^{10}$ pCi ($6.0 \times 10^{8}$ Bq) radon-222/kg body weight in equilibrium with its decay products

(Hollcroft et al. 1955). Renal failure may have caused the observed anemia (see Hematological Effects), weight loss (see Other Effects), and decrease in lifespan observed in these mice. (See Section 2.2.4.1 for limitations of Hollcroft et al. 1955.)

**Other Effects.** A single intravenous injection of radon at a concentration of $1.6 \times 10^{10}$ pCi ($6.0 \times 10^{8}$ Bq) radon-222/kg body weight in equilibrium with its decay products resulted in a decrease in body weight in mice, possibly due *to* renal failure (Hollcroft et al. 1955). (See Section 2.2.4.1 for limitations of Hollcroft et al. 1955.)

No studies were located regarding the following effects in humans or animals after exposure to radon and radon daughters by other routes.

**2.2.4.3 Immunological Effects**
**2.2.4.4 Neurological Effects**
**2.2.4.5 Developmental Effects**
**2.2.4.6 Reproductive Effects**
**2.2.4.7 Genotoxic Effects**
**2.2.4.8 Cancer**

## 2.3 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 daughters is accomplished by modeling the sequence of events involved in the inhalation, deposition, clearance, and decay of radon daughters within the lung. While based on the current understanding of lung morphometry and experimental data on radon and radon daughter toxicokinetics, 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 Bair (1985), BEIR IV (1988), EPA (1988a), ICRP (1978), James (1987), NEA (1983), and NCRP (1984).

In this section the toxicokinetics of radon is described based on the available experimental data rather than descriptions derived from models. The toxicokinetics of radon, as it relates to the development of adverse health effects in exposed populations, is further complicated by the transformation of radon to radon daughters. These progeny may be present with radon in the environment and inhaled or ingested along with radon and/or they may be formed in situ from the transformation of the radon absorbed in the body.

### 2.3.1 Absorption

#### 2.3.1.1 Inhalation Exposure

The primary route of exposure to radon and its progeny is inhalation. The degree of deposition and the subsequent absorption of inhaled radon and progeny is determined by physiological parameters, such as respiration rate and tidal volume; and physical properties, such as the particle size distribution of the carrier aerosols and of the unattached fraction, the equilibrium state, and solubility coefficients (Crawford-Brown 1987; Holleman et al. 1969; Jacobi 1964).

Since radon is an inert gas, its movement across membranes is driven by solubility coefficients (Crawford-Brown 1987) and it may be readily absorbed by crossing the alveolar membrane. Most inhaled radon will be exhaled before it can decay and deposit a significant radiation dose to the lung tissue, due to the relatively long half-life of radon gas (McPherson 1980).

The radioactive decay of radon results in the formation of long- and short-lived daughter products which may attach to the surface of aerosol particles and, when inhaled, deposit on the mucus lining of the respiratory tract through impaction, sedimentation, or diffusion (Altshuler et/al. 1964). It is assumed that the short-lived daughters, polonium-218, lead-214, and bismuth-214, remain in the mucus layer (James 1987); however, absorption of deposited radon daughters from the lung into the blood stream also may occur (Jacobi 1964; Morken and Scott 1966). The deposited radon daughters appear to act as soluble substances and are released from the dust particles after they undergo solvation (ICRP 1966). The long-lived radon daughter products (lead-210, bismuth-210, and polonium-210) contribute little to the radiation dose to lung tissue because they have a greater likelihood of being physically removed by ciliary action or absorbed by macrophages before they can decay and deliver a significant radiation dose (McPherson 1980). The absorption characteristics and rates of mucus clearance in various parts of the respiratory tract are uncertain (James 1987).

The total respiratory deposition of radon daughters in human subjects has been determined experimentally by George and Breslin (1967, 1969), Holleman et al. (1969), and Shapiro (1956) to range from 18% to 51% of the inhaled amount and to be dependent on tidal volume, particle size, and breathing rate. In general, deposition increases with increasing tidal volume, with smaller particle size, and with changes in normal breathing rates. Respiratory deposition has also been measured in casts of the human larynx and trachea by Chamberlain and Dyson (1956) who determined an average deposition of about 22% of the inhaled, uncombined radon activity at a breathing rate of 20 L/minute. The important sites for deposition of aerosols were determined by the use of casts of the human tracheobronchial tree to be at or near the first bifurcations of the bronchi (Cohen 1987; Martin and Jacobi 1972). According to Cohen (1987), the nonuniform deposition for bifurcations as compar,ed with airway lengths suggests that the dose from radon daughter deposition will be

about 20% greater than estimated for uniform deposition. Estimation of dose to the respiratory tract has been extensively studied using models (BEIR IV, 1988; EPA 1989a; Harley and Pasternak 1982). Both the studies of human lung casts and the information derived from models indicate that most deposition occurs in the tracheobronchial region of the lung; other regions (nasopharyngeal and pulmonary) receive much smaller doses (BEIR IV 1988).

From a study in rats, Cohn et al. (1953) were able to conclude that the radiation exposure per unit area is greater for the bronchi than for any other lung tissue and, that the radiation dose to the respiratory tract from the progeny was 125 times greater than from radon alone.

#### 2.3.1.2 Oral Exposure

Exposure to radon by the oral route occurs from dissolution of radon in drinking water and, of the total radon dissolved in water, 30% to 70% may be lost by aeration and would be available for inhalation (Dundulis et al. 1984; Holoway and Turner 1981). Another study reported a loss of 15% to 25% radon to the air from drinking (Suomela and Kahlos 1972). Based on the time-course of radon elimination in expired air, it appears that the majority of radon absorption following ingestion in water occurs in the stomach and small intestine, and only 1% to 3% of the ingested radon remains to enter the large intestine to be available for absorption (Dundulis et al. 1984). Studies with other inert gases indicated that the small intestine plays a major role in gastrointestinal uptake of these inert gases (Tobias et al. 1949).

The rate of absorption of radon from the gastrointestinal tract depends on the stomach contents and the vehicle in which it is dissolved. Experimental data from humans who ingested radon dissolved in water indicate that radon is rapidly absorbed from the stomach and small intestines, and that greater than 90% of the absorbed dose is eliminated by exhalation in less than 1 hour (Hursh et al. 1965). Absorption of radon also may occur in the large intestine. This is based on experimental data where exhalation of radon continues at lower concentrations for a longer time after administration when radon dissolved in drinking water is ingested on a full stomach as compared to ingestion of radon on an empty stomach (Meyer 1937). The absorption of radon following ingestion of a meal high in fat is delayed (Vaternahm 1922). Radon is present in exhaled air at higher concentrations and at later times after ingestion of oil or fat emulsions containing radon than with water containing radon (Vaternahm 1922).

Ingested radon progeny may not contribute significantly to the radiation dose to the stomach as they may not penetrate the mucus lining to a great extent (Von Dobeln and Lindell 1964). Production of daughter products *in situ*, following absorption of radon in the gastrointestinal tract, will primarily result in a radiation dose to the gastrointestinal wall (Von Dobeln and Lindell 1964). The ingestion of radon may also result in exposure to lung tissue due to absorption from the gastrointestinal tract with transport by way

of the systemic circulation to the lung with subsequent decay to daughter products occurring in the lung (Crawford-Brown 1987).

#### 2.3.1.3 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 to 15 minutes, radon-222 concentrations in expired air reached approximately 0.9% of that in the water and ranged from 17.9 to 49.1 pCi radon-222/L of air (662 to 1817 Bq/$m^3$) compared to pre-bath levels of less than 1 pCi radon-222/L of air (37 Bq/$m^3$). Radon concentrations in the water were reported by the authors as 5,800 pCi (215 Bq) radon-222/kg. However, the relative contributions of the dermal and inhalation routes cannot be determined (Furuno 1979). Radon concentrations in blood reached 0.85% to 1% of the radon concentration in the bath water, which was $1.8x10^5$ pCi (4.9x106 Bq) radon-222/L of water, after 30 to 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).

#### 2.3.1.4 Other Routes of Exposure

No studies were located regarding absorption of radon or its progeny in humans and laboratory animals after exposure by other routes.

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

The distribution of radon once it is absorbed or deposited in the lung is a function of its physical properties. Radon progeny, especially the longlived daughters, that have been deposited in the lungs are partially removed by the mucociliary blanket, which then carries the particles to the trachea and the gastrointestinal tract. Following chronic exposure in humans, lead-210, a stable daughter product, has been found in bone (Black et al. 1968; Blanchard et al. 1969; Cohen et al. 1973; Fry et al. 1983) and in teeth (Clemente et al. 1982, 1984). After prolonged exposure, radon concentrations in body organs can reach 30% to 40% of inhaled concentrations (Pohl 1964).

Fat appears to be the main storage compartment in rats following inhalation exposure. In rats following an acute exposure to radon, concentrations of radon and radon daughters were much higher in the omental fat than in any of the other tissues examined, followed by the venous blood, brain, liver, kidney, heart, muscle tissues, and testes (Nussbaum and Hursh 1957). Radon reached equilibrium in the fat in about 6 hours compared to 1 hour in all other tissues. This may be due to the nonuniformity of blood perfusion within this tissue.

### 2.3.2.2 Oral Exposure

After radon enters the gastrointestinal tract, it is absorbed into the blood stream and then distributes to different organs and tissues (Crawford-Brown 1987). This transfer from the gastrointestinal tract to the blood was dependent upon the emptying patterns of the stomach into the upper intestine, stomach content, fat content of meals, and time of meal in relation to radon ingestion (Hursh et al. 1965; Suomela and Kahlos 1972; Vaternahm 1922; Von Dobeln and Lindell 1964). No age-dependent differences in radon distribution from the gastrointestinal tract should be evident due to rapid equilibration in the body (Crawford-Brown 1983). However, changes in the mass of fatty tissue would be expected to affect distribution processes since radon is more soluble in fat than in other tissues (Crawford-Brown 1987).

According to Hursh et al. (1965), in humans greater than 90% of ingested radon is distributed to the lung where it is rapidly exhaled. Of the remaining administered dose of radon, 5% is distributed to the liver, 1.6% to the kidneys, and 2% to lung tissue (Holoway and Turner 1981). Acute exposure of human subjects to $1.3 \times 10^{5}$ to $2.83 \times 10^{5}$ pCi ($4.9 \times 10^{3}$ to $1.05 \times 10^{2}$ Bq) radon-222/L of water resulted in a whole body accumulation of $1.9 \times 10^{3}$ to $1.22 \times 10^{4}$ pCi (70 to 450 Bq) bismuth-214, a radon decay product. The biological halflife of radon in these individuals ranged from 30 to 50 minutes (Suomela and Kahlos 1972).

From a chronic study in laboratory animals where 3.6 pCi (0.13 Bq) of radon was administered daily for 1 year, a body accumulation of 5 pCi (0.19 Bq) lead-210/g of tissue, 0.08 pCi ($3.0 \times 10^{-3}$ Bq) polonium-210/g of tissue, and 0.003 pCi ($1.1 \times 10^{-4}$ Bq) bismuth-210/g of tissue was reported (Fernau and Smereker 1933). Radon is very soluble in fat with its distribution coefficient in fat greater than in any other organ or tissue (Nussbaum and Hursh 1957). This storage of radon in body fat is a constant source of lead-210, polonium-210, and other progeny (Djuric et al. 1964). The presence of lead-210 and polonium-210 are not unique to radon exposure and are also found in cigarette smoke and food (NCRP 1984b).

In addition to the available data on distribution in humans and laboratory animals, many different models exist which estimate distribution in humans (EPA 1988a; ICRP 1978).

### 2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or laboratory animals after dermal exposure to radon or its progeny.

### 2.3.2.4 Other Routes of Exposure

No studies were located regarding distribution of radon or its progeny in humans or laboratory animals after exposure by other routes.

### 2.3.3 Metabolism

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

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

Most of the inhaled radon will be eliminated by exhalation before it can decay and deposit a significant radiation dose to the lung tissue. The longlived radon progeny are, to some extent, physically removed before they can decay and deposit a radiation dose (McPherson 1980). The biological half-time for radon daughters in the pulmonary region has been reported to range from 6 to 60 hours and in the tracheobronchial region to range from 10 minutes to 4.8 hours (Altshuler et al. 1964; Jacobi 1964, 1972). The biological half-time in fat tissue has two components, a fast component of 21 minutes and a slow component of 130 minutes (Nussbaum and Hursh 1957).

Long-lived radon progeny (lead-210) have been reported to be excreted in the urine of uranium miners at 1 to 18 years following exposure. This excretion of lead-210 results from a slow release of the daughters from bone. Concentration of lead-210 in bone has been shown to correlate with cumulative exposure to radon and radon daughters in WLM (Black et al. 1968).

Experiments in rats and mice indicated that polonium-214 may be retained in the lung following inhalation exposure. The retention efficiency of polonium-214, a stable daughter product, in the lung was 2% and 2.2% of the administered activity in rats and mice, respectively, immediately following acute inhalation exposure (Doke et al. 1973).

#### 2.3.4.2 Oral Exposure

Following ingestion of radon dissolved in water, greater than 90% of the absorbed radon was eliminated by exhalation within 100 minutes. By 600 minutes, only 1% of the absorbed amount remained in the body (Hursh et al. 1965). The biological half-time for removal of radon from the body ranges from 30 to 70 minutes depending on whether the stomach is empty or full and on fat content in the diet (Hursh et al. 1965; Suomela and Kahlos 1972; Vaternahm 1922). The presence of food in the stomach may result in a marked delay in the removal of radon from the body due to an increased emptying time of the stomach during which time a portion of the radon may decay (Hursh et al. 1965). The biological half-life in the blood of humans has been reported to be 18 minutes for 95% of the administered dose and 180 minutes for the remaining 5% (Hursh et al. 1965). The longer half-life for the remaining 5% may be due to storage and subsequent removal from tissues. The effective half-life for removal of radon was reported as 30 minutes (Andersson and Nilsson 1964).

The transfer rate of radon from the gastrointestinal tract and subsequent elimination from the respiratory tract was found to be dependent on the pattern of emptying of the stomach into the small intestines (i.e., with or without a meal), and the accompanying vehicle (i.e., water or fat). After ingestion of radon dissolved in drinking water on an empty stomach, radon in exhaled air rapidly increased reaching a maximum concentration in exhaled air 5 to 10 minutes after ingestion (Meyer 1937). With ingestion of radon in drinking water with or after a meal, radon elimination in expired air is delayed and varies in concentration with time, reflecting absorption from the small intestines as it receives a portion of the stomach contents (i.e., with stomach emptying patterns) (Meyer 1937). After ingestion of radon dissolved in olive oil on an empty stomach, elimination in expired air reached a maximum concentration 50 minutes post-ingestion, then declined; however, when administered in olive oil after a meal, radon in expired air remained constant from 10 minutes to 5 hours after ingestion (Vaternahn 1922). These data suggest that radon is eliminated in expired air more rapidly from a water vehicle than a fat or oil vehicle and this elimination occurs over a longer period of time when ingested with a meal than on an empty stomach.

When radon dissolved in water was ingested on a full stomach, the exhalation of radon reached a maximum at 5 to 15 minutes then declined. This was then followed by a second peak about 20 minutes after ingestion. When ingestion of radon occurred “some time”after a meal, the second radon peak in exhaled air was delayed and was followed by further peaks (Meyer 1937). These subsequent peaks were explained by the absorption of radon from the intestine after it has received portions of the stomach content (Meyer 1937).

#### 2.3.4.3 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 radoncontaining water had exhaled approximately one-third of radon measured in blood immediately after bathing (Pohl 1965). By 6 to 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.

#### 2.3.4.4 Other Routes of Exposure

Experiments in animals have reported the retention of radon after exposure by the intraperitoneal and intravenous routes. After intravenous administration, 1.6% to 5.0% of the administered activity was retained in the animals after 120 minutes (Hollcroft and Lorenz 1949). Retention was greatest after intraperitoneal administration at 120 minutes, 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 after intravenous administration of radium-226. The amount of radon in bone was found to increase with increasing time after injection (Mays et al. 1975).

## 2.4 RELEVANCE TO PUBLIC HEALTH

Growing concern in the late 1940s that the inhalation of radon and radon daughters was contributing to the adverse health effects observed in underground miners stimulated the conduct of epidemiological investigations and initiated animal studies with radon and radon daughters. Earlier inhalation studies had been conducted with radon only, but evidence from radon dosimetry studies indicated the involvement of radon daughters rather than just radon (Bale 1951). Epidemiological studies further suggested that the major health effects observed in miners might be attributed to radon daughters. Both human and animal studies indicate that the lung and respiratory system are the primary targets of radon daughter-induced toxicity. The evidence indicates that inhalation of radon decay products results in radiation damage to tissues in which these products are deposited. Nonneoplastic respiratory disease and lung cancer have been reported in humans and animals exposed to radon and radon daughters by inhalation.

**Death.** No deaths in humans following acute exposure to radon have been reported. Following long-term exposure, significant increases in early mortality due to nonneoplastic respiratory diseases have been reported among uranium miners. Because mortality due to nonneoplastic diseases is not generally reported by exposure categories (i.e., WLM categories), it is not clear what exposure concentration or duration of exposure in these mining cohorts is associated with this increased mortality. In addition, these nonneoplastic respiratory deaths cannot be attributed solely to radon but may result from exposure to other mine air pollutants. Reduction in lifespan due to respiratory disease as a result of exposure to high levels of radon or radon daughters has been reported in various animal studies. Based on the evidence in animals, it is apparent that death due to respiratory disease may result after exposure to radon at very high levels. However, it is unclear to what extent low-level environmental exposure to radon and radon daughters may increase the risk of death due to nonneoplastic respiratory disease.

**Respiratory Effects.** Respiratory disease characterized as emphysema, fibrosis, or pneumonia has been reported in both humans and animals with inhalation exposure to high levels of radon and radon daughters. In addition to deaths due to nonneoplastic respiratory disease, some studies have reported reductions in respiratory function. In all of the occupational cohorts, miners were concomitantly exposed to other mine pollutants, such as ore dust, other minerals, or diesel-engine exhaust. The contribution of these pollutants, as well as cigarette smoking, to the induction of nonneoplastic respiratory disease is unclear. As reported in Section 2.6, Interactions With Other Chemicals, the combination of radon and radon daughters along with ore

dust or other pollutants enhanced the incidence and severity of adverse respiratory effects in laboratory animals as compared to either toxicant alone. Induction of this type of respiratory disease may occur primarily at doses that exceed those commonly found in the environmental setting; however, the radiation dose that would result in either pulmonary dysfunction or pulmonary disease is not known. The adverse respiratory effects observed appear to be consistent with alpha radiation damage that may occur at high doses in slower regenerating tissues such as the lung (see Appendix B). That being the case, production of respiratory tissue damage in the lungs may not be immediately apparent, especially at low environmental exposures.

**Hematological Effects.** No information on the hematological effects of radon in humans was located in the available literature. Alterations in hematological parameters following exposure to radon have been reported in animals. The extent and severity of the hematological effects were related to the level of exposure and the exposure duration, and red blood cells appear to be more sensitive to the effects of radon than white blood cells. Following acute exposure by the inhalation or intravenous routes, decreases in the number of red blood cells and white blood cells occurred immediately postexposure. Red blood cells remained depressed for the remaining life of the treated animals, while white blood cells returned to normal levels postexposure. Following repeated exposures, white blood cell counts remained depressed for longer periods of time and, with chronic exposure, depression in white blood cell counts was linearly related to the cumulative exposure. The animal studies indicate chronic exposure of humans to radon may result in similar alterations in the hematopoietic system.

**Renal Effects**. Evidence of kidney disease has been reported in United States uranium miners (Waxweiler et al. 1981). In that survey, chronic and unspecified nephritis was elevated after a lo-year latency. The nephrotoxicity of soluble uranium in animals has been documented (ATSDR 1990a). Due to their relatively short half-lives, the alpha-emitting radon daughters present in the lung undergo radioactive decay before they move to other organs, in contrast to other alpha-emitting radionuclides, such as uranium or plutonium (ATSDR 1990a, 1990b), which may translocate from the lung to irradiate other tissues. Nevertheless, direct evidence of renal dysfunction or impairment resulting from inhalation or oral exposure to radon and radon daughters alone is lacking.

**Neurological Effects.** No information on neurological effects in humans exposed to radon was located in the available literature. Only one animal study attributed the toxic effects observed to the action of radon on the central nervous system. This study reported respiratory paralysis due to central nervous system depression; however, the study has numerous flaws (see Section 2.2.1.4) that limit its usefulness and render the reported results questionable.

**Reproductive Effects.** Recent epidemiological studies have raised speculation that inhalation exposure to radon and radon daughters during uranium mining may be associated with effects on reproductive outcome. A decrease in the secondary sex ratio (the ratio of male to female children) of children of underground miners following employment in uranium mines was reported (Dean 1981; Muller et al. 1967). Waxweiler and Roscoe (1981), however, found the secondary sex ratio to increase in older men but to decrease in younger men. If the father is exposed to radiation, an increase in the number of male children might be expected due to the relative resistance of the Y chromosome as compared to the X chromosome (Waxweiler and Roscoe 1981). In a preliminary study, Wiese and Skipper (1986) reported a decrease in the secondary sex ratio, although not statistically significant, in children born to underground uranium and potash workers. No other information exists on reproductive effects in other epidemiological investigations or animal studies. Therefore, these observations of alterations in secondary sex ratios are suggestive of possible effects but are not conclusive evidence that radon can produce reproductive toxicity in persons environmentally exposed to radon.

**Genotoxic Effects.** Increases in chromosomal aberrations have been reported among uranium miners and among personnel employed at a radon spa in Austria following inhalation exposure. Increases in chromosomal aberrations were also reported in a small group of people living in an area with high radon concentrations in their water supply. As stated in Section 2.3 on toxicokinetics, radon rapidly escapes from water; therefore, the probable major route of exposure in this cohort also was inhalation. In addition, increased DNA-repair rates in lymphocytes were observed in another occupational cohort. The increased DNA repair rates may reflect increases in DNA damage. DNA repair enzymes may be induced in response to DNA damage. The implications of this information for environmental exposures are unclear. In the case of the miner occupational cohorts, cumulative exposures were greater than 100 WLM and ranged up to 6,000 WLM. Also, the animal data are inconclusive and do not clearly establish a link between genotoxicity and radon exposure. A summary of the genotoxicity studies is given in Table 2-2.

**Cancer.** Numerous epidemiological studies have demonstrated a causal association between lung cancer mortality and exposure to radon in combination with radon daughters. The majority of these epidemiological data have been collected from occupational cohorts exposed to radon and radon daughters during mining operations. Despite the variety of conditions reported for the mines (including dust concentrations, type of ore mined, and ventilation rates) and differences in the cohorts (including levels of exposure, length of follow-up, smoking habits, and ages of exposure), exposure to radon in mining operations is clearly directly associated with lung cancer mortality.

Some of these studies indicate that lung cancer mortality was influenced by the total cumulative radiation exposure, by the age at first exposure, and by the time-course of the exposure accumulation. The length of the induction

TABLE 2-2. Genotoxicity of Radon-222 In Vivo

| End Point | Species (Test System) | Result | Reference |
|---|---|---|---|
| MAMMALIAN SYSTEMS | | | |
| *Chromosomal aberrations* | *Human (peripheral lymphocytes)* | + | Pohl-Rüling et al. 1976, 1987; Pohl-Rüling and Fischer 1979, 1982, 1983; Brandom et al. 1972, 1978 |
| | Human (whole body lymphocytes) | + | Stenstrand et al. 1979 |
| | Rabbit (somatic cells) | - | Leonard et al. 1981 |
| DNA repair | Human (lymphocytes) | + | Tuschl et al. 1980 |
| Sister chromatid exchanges | Rat (bone marrow cells | + | Poncy et al. 1980 |
| INVERTEBRATE SYSTEMS | | | |
| Dominant lethal | Drosophila melanogaster | (+) | Sperlich et al. 1967 |

+ = positive result
- = negative result
(+) = positive or marginal result

latency, that is, the time from the start of mining to the development of cancer, is strongly dependent on the age at which a man starts mining (Archer 1981). The data indicate that the older a man is when he starts mining, the shorter his induction-latency period will be. The Czechoslovakian data indicate that the frequency of attributable lung cancer mortality rises steeply with increasing age at the start of mining, corresponding to decreasing induction-latency periods (Sevc et al. 1988). There is evidence that the induction-latency period is also dependent on the exposure rate and total radiation exposure, that is, the lower the exposure rate, the longer a group must be followed to evaluate the lung cancer risk (Archer et al. 1979). According to Sevc et al. (1988) lung cancer mortality for the same cumulative WLMs was greater in the subcohort with higher exposures early in their work history, compared to those with nearly equal yearly exposure or the subcohort with lower initial exposure which increased to higher levels in later years. Additional support for the role of radon as a causative agent in lung cancer is provided by the results of the studies of nonuranium hard rock miners, which also showed an increased mortality rate from lung cancer.

Some of these studies also indicated that underground miners who were cigarette smokers had a higher incidence of radiation-induced lung cancer mortality than did miners who were nonsmokers, and that the induction-latency period was substantially shorter for smokers than for nonsmokers (Archer 1981). A study of a nonsmoking cohort of uranium miners clearly indicated an increased mortality risk for lung cancer for the cohort (Roscoe et al. 1989). In addition, increases in lung cancer among American Indian uranium miners, who had a low frequency of lung cancer in the nonexposed general population compared to rates in the white United States population and a low frequency of cigarette smoking, support the conclusion that radiation is the primary cause of lung cancer among uranium miners (Gottlieb and Husen 1982; Samet et al. 1984b; Sevc et al. 1988). A comprehensive evaluation of risk estimates from various mining cohorts can be found in BEIR IV (1988).

Several studies of residential exposure to radon and radon daughters also indicate an increased risk of lung cancer (Axelson and Edling 1980; Axelson et al. 1971, 1981; Edling et al. 1984; Svennson et al. 1987, 1989). These studies are primarily case-control studies that involve a small number of subjects and have exposure estimates that are limited or based on surrogates. A more recent study has reported on a much larger cohort and has provided some exposure information (Svennson et al. 1989). These studies support the evidence obtained from the occupational cohorts. Radon concentrations in environmental settings are not expected to be at levels as high as those encountered in mining operations nor would they be expected to be combined with dusty conditions or diesel exhaust exposure, two features of the exposure of several of the examined cohorts. However, the BEIR IV (1988) Committee indicated that the risk from occupational or residential exposure to radon is the same per unit dose.

Studies in animals confirm and support the conclusions drawn from the epidemiological data. When all animal data are combined and reviewed, four

variables surface which appear to influence the efficiency of radon daughters to produce lung cancer in laboratory animals (Cross et al. 1984). These variables include: cumulative exposure to radon and radon daughters, exposure rate to radon and radon daughters, unattached fraction of radon daughters, and disequilibrium of radon daughters. Another factor which may influence the tumorigenic potential of radon and radon daughters is exposure in conjunction with other pollutants, such as uranium ore dust or cigarette smoke (see Section 2.6 for a discussion of interactions of radon with other chemicals). The ability of radon daughters, alone or in conjunction with uranium ore dusts, to produce lung tumors in laboratory animals appears to increase with an increase in exposure until lifespan shortening reverses the trend, with a decrease from high exposure rate to low exposure rate, and with increasing unattached fraction and disequilibrium.

In general, the pattern of results from the epidemiological studies and animal experiments clearly indicates a risk due to radon and radon daughter exposure. Although individual studies have particular shortcomings that may make that conclusion less supportable for the individual study, the pattern over all the studies is convincing. Positive associations between exposure to radon daughters and lung cancer have been found in occupational settings for various types of mining operations, in various ethnic groups around the world, and under various concomitant exposure conditions. In some of these occupational settings, concomitant exposure to other pollutants, such as ore dust, diesel engine exhaust, or other minerals, such as silica, may have occurred. The possible impact of these other pollutants on radon daughterinduced lung cancer is unclear (see Section 2.6).

## 2.5 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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid 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 (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 biologic 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 2.5.1.

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 epithelium cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not 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 2.5.2.

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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

### 2.5.1 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, and can be measured 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 indicate exposure to radon, exposure to uranium or radium may also result in the presence of these decay products. Polonium-210 may also be found in tissues after exposure to cigarette smoke. Levels of lead-210 in teeth have been associated with levels of radon in the environment in an area with high natural background levels of radon and radon daughters (Clemente et al. 1984). In addition, Black et al. (1968) reported correlation of radiation exposure and lead-210 levels in bone from uranium miners. However, cumulative exposure to these individuals was estimated. Biomarkers of radon or radon progeny exposure 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-222 from levels of stable radon daughter products, lead-210 and polonium-210, 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 progeny. Quantification of exposure to radon is further complicated by the fact that radon is an ubiquitous substance and background levels of radon and radon progeny are needed to quantify higher than "average" exposures.

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Radon

The principal target organ identified in both human and animal studies following exposure to radon and 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 radon daughters (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 xenobiotics such as cigarette smoke. In addition, even though increases in the frequency of abnormal sputum cytology can be measured, they may not provide a reliable correlation between levels in human tissues or fluids with health effects in exposed individuals.

A dose-response relationship between chromosome aberrations and increased environmental levels of radon has been reported (Pohl-Rtiling and Fischer 1983; Pohl-Riiling et al. 1976, 1987). Although the presence of chromosome aberrations is a biomarker of effect, the potential range of chemicals which could cause this effect is so great that it would not necessarily be considered radon-specific.

Additional biomarkers of effect for radon and radon progeny exposure may exist; however, these were not located in the reviewed literature. For more information on biomarkers for effects of the immune, renal, and hepatic systems see ATSDR, CDC Subcommittee Report on Biological Indicators of Organ Damage (1990c) and for biomarkers of effect for the neurological system see OTA (1990). For more information on health effects following exposure to radon and radon daughters see Section 2.2.

## 2.6 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 radon daughters 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 radon daughters (US DHHS 1985). Studies by Lundin et al. (1969, 1971) reported 10 times more lung cancer among United States uranium miners who smoked. In a case-control study of United States uranium miners, Archer (1985) reported that smoking miners with lung cancer had significantly reduced latencyinduction 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 the possible synergistic or additive effect between radon and radon daughters and cigarette smoking (Klassen et al. 1986). However, an antagonistic relationship between cigarette smoking and lung cancer in humans may exist according to Sterling (1983). His hypothesis is that smokers may have a lower potential retention of deposited radon daughter particles due to enhanced mucociliary clearance. Other investigators have reported that nonsmoking miners exhibited a higher incidence of lung cancer than smokers, although the latency of cancer induction was shorter in nonsmokers than for smokers (Axelson 1980; Axelson and Sundell 1978). Again, the theories put forth to explain this phenomenon include increased mucus production and alterations in mucociliary clearance in smokers resulting in the increased mucus thickness.

Some animal studies support the theory that cigarette smoke potentiates the effects of radon and radon daughters 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 radon daughters 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 daughters plus uranium ore dust, compared to animals exposed to only radon daughters plus uranium ore (Filipy et al. 1974). In contrast, some studies suggest an antagonistic interaction between smoking and radon daughter-induced lung cancer. Dogs exposed daily to cigarette smoke followed immediately by exposure to radon and radon daughters and uranium ore dust exhibited a decrease in the incidence of lung tumors, compared to dogs exposed to radon and radon daughters 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 radon daughters 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 with cerium hydroxide (Chameaud et al. 1974).

Other airborne irritants, as well as ore dust and diesel exhaust, may act synergistically with radon and radon daughters 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 (Sevc 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; Sevc 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. 1981, 1982b, 1984; Pacific Northwest Laboratory 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 radon daughters 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 radon daughters. 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 radon daughters 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 radon daughters, 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 radon daughters in conjunction with silicon dioxide increased the incidence of nodular fibrosis of the lungs in rats (Kushneva 1959).

## 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Children may be more susceptible to the effects of radon and radon daughters. Differences in lung morphometry and breathing rates in children result in higher estimated doses that may make children more susceptible to the effects of radon than adults (Samet et al. 1989). In calculating the inhaled dose of radon, Hofmann et al. (1979) reported that dose was strongly dependent on age, with a maximum value reached at about the age of 6 years. Risk of cancer from exposure to low levels of ionizing radiation during childhood are estimated to be twice that of adults (BEIR V 1990). Risk of lung cancer in children resulting from exposure to radon may be almost twice as high as the risk to adults exposed to the same amount of radon (NCRP 1984a).

Populations that may be more susceptible to the respiratory effects of radon and radon daughters 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. In addition, persons who have existing lung lesions may be more susceptible to the tumor-causing effects of radon (Morken 1973).

## 2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 2.8.1 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 and radon daughters are summarized in Figure 2-2. 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 imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Figure 2-2 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 radon daughters. No information on the health effects of radon and radon daughters in humans was available following acute or intermediate exposure by any route. No information on the health effects of radon and radon daughters 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.

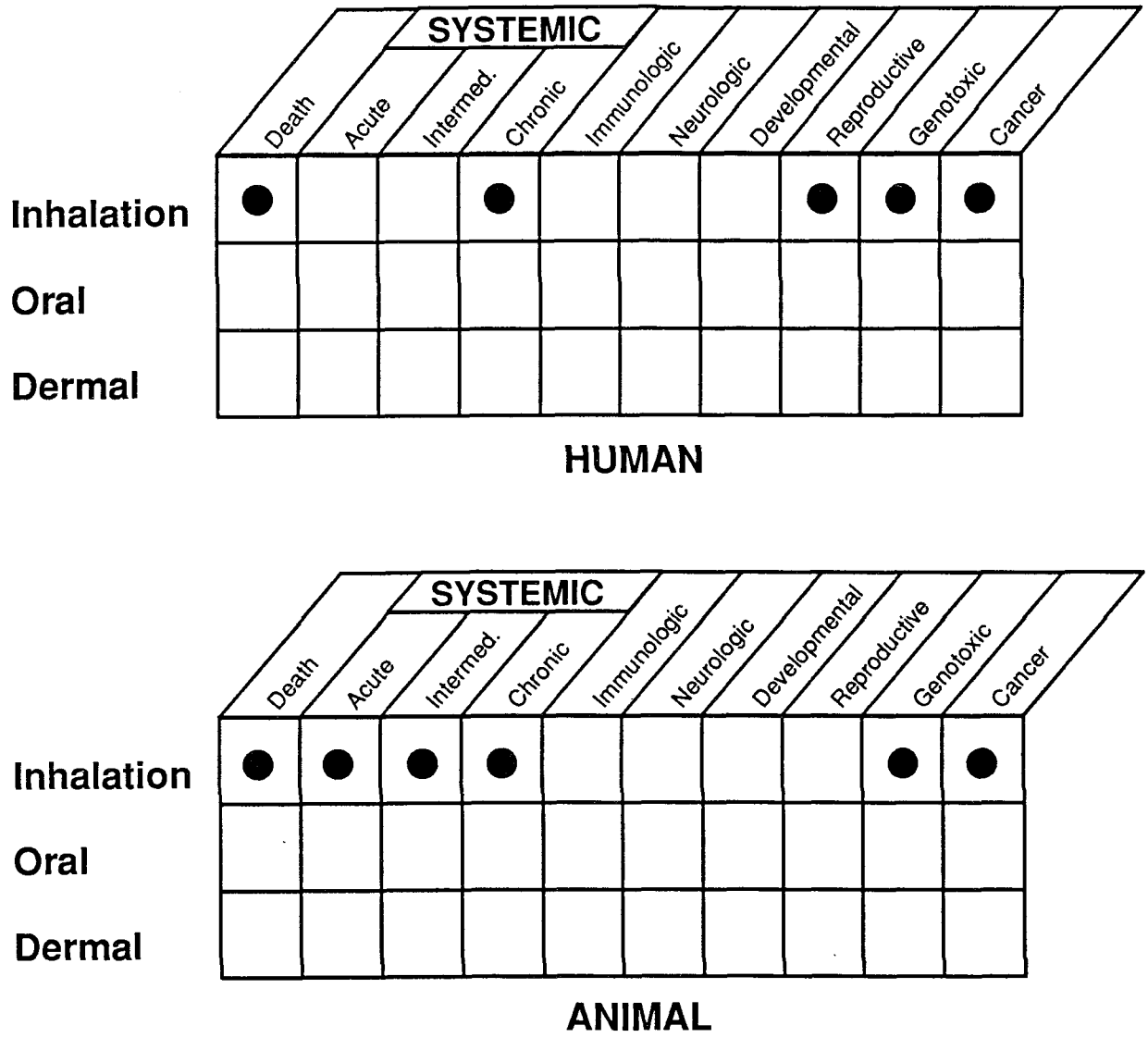


**FIGURE 2-2. Existing Information on Health Effects of Radon**

### 2.8.2 Identification of Data Needs

**Acute-Duration Exposure.** No information exists regarding the health effects to humans following their acute exposure to radon and radon daughters 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 acute exposure to lower levels of radon. This information is needed in order to assess the toxicity of radon.

**Intermediate-Duration Exposure.** No information regarding health effects following intermediate-duration exposure to humans by any route was clearly identified in the available literature. Epidemiological studies in general focused on cohorts exposed to radon and radon daughters for durations longer than one year. Animal studies demonstrate that intermediate exposure to high levels of radon and radon daughters resulted in chronic respiratory toxicity and lung cancers. This is an indication of the potential for such effects in exposed human populations. 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 on toxicity to other organs, other than the respiratory tract 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. Carefully designed studies in which laboratory animals are exposed to levels that are similar to high environmental levels for partial lifetime and observed for life could provide important information. These studies would facilitate the estimation of cancer risk to persons living in an area with high natural levels for only a portion of their life. These animal studies should address both the effect of total dose and dose-rate on development of adverse health effects. This information may also be useful in situations in which the time lapse between identifying the presence of radon and any remediation effort is of an intermediate duration.

**Chronic-Duration Exposure and Cancer.** Knowledge of the adverse health effects in humans following chronic radon and radon daughter exposure is based primarily on studies in adult male underground miners. These studies describe predominantly respiratory end points, such as emphysema, fibrosis, and cancer. To a large extent other health effects have not been studied. Epidemiological studies in general report only the cause of death for each member of the cohort; therefore, there is insufficient information on whether other adverse effects were identified other than the ones listed as cause of death. Little or no information exists on cardiovascular, gastrointestinal, renal, musculoskeletal, immunological, or dermal/ocular effects in humans or animals. In addition, these miners also may have been simultaneously exposed to other pollutants (e.g., long-lived radioactive dusts (uranium), diesel-engine

exhaust, cigarette smoke, and external gamma radiation). Several of these factors have been implicated independently as causative agents of lung cancer and respiratory diseases and the excess lung cancers in cigarette smokers have been well documented. Thus, the data currently used to characterize a human health hazard with regard to respiratory toxicity represent a composite response to other factors as well as to radon daughters.

Chronic exposure to radon and radon daughters in laboratory animals also results in respiratory lesions. In laboratory animals exposed to radon and radon daughters in combination with uranium ore dust, pulmonary fibrosis and emphysema have resulted. Further research of the interaction of radon and radon daughters with other environmental pollutants, especially cigarette smoke, is needed. This information could be used to clarify uncertainties in the extrapolation of the data in miners to describe the potential hazard to human health from environmental radon daughter exposures. Well-defined studies that examine both pathological and functional changes in other organ systems are necessary to clarify these issues.

Radon dissolved in drinking water is a source of human exposure. Studies are needed which describe the absorption and translocation of radon gas and the effects of alpha radiation emitted by radon daughters at the site of entry, the gastrointestinal tract. While translocation of radon daughters from the portal of entry to other sites in the body may be limited (due primarily to the short half-life of most alpha emitting radon daughters), radon gas may distribute to other organs and, thereby, provide an internal source of radon daughter alpha radiation.

Epidemiological studies have demonstrated a causal association between exposure to radon and radon daughters and lung cancer mortality. The number of lung cancer mortality cases in these cohorts was influenced by the total cumulative radiation exposure, by the age at first exposure, and by the time course of the exposure duration. Significant increases in lung cancer that were demonstrated in chronic studies in mice, rats, and dogs resulted from exposure of these animals to radon and radon daughters in combination with one or more other pollutants, such as uranium ore dust, diesel-engine exhaust, or cigarette smoke. Chronic studies in hamsters (Pacific Northwest Laboratories 1978) in which animals were exposed to radon and radon daughters alone did not demonstrate a significant carcinogenic response; however, the hamster may be resistant to radiation-induced lung cancer. Hamsters did not develop lung tumors when exposed to another alpha-emitter, plutonium (ATSDR 1990b). Evidence from animal studies indicates that factors such as the unattached fraction and disequilibrium of radon daughters influence lung cancer production. Other air pollutants may interact synergistically with radon daughters in lung tumor induction. Long-term studies designed to evaluate the potential interaction of radon daughters with other pollutants would provide information necessary to determine the toxicity of radon and radon daughters. Factorial studies, i.e., studies that test radon and radon daughters alone and radon and radon daughters with only one other confounding factor are needed because much of the cancer information to date is from studies with several

confounding factors. These studies could help elucidate the extent of interaction between radon and each confounding factor.

**Genotoxicity.** Studies of miners and other populations exposed to radon and radon daughters showed an increased occurrence of chromosomal abnormalities. However, because exposure-effect relationships have not yet been established and the biological significance of these chromosomal effects is uncertain, further studies should be performed. In vitro studies using human cell lines could help determine a dose-response for exposure to radon and radon daughters and increased chromosomal abnormalities. Such relationships may be difficult to establish because of possible interactions with other substances, i.e., uranium ore dust. There are no in vivo animal data to support the observed increase in chromosomal abnormalities in human populations. Further observations in laboratory animals are needed to explain these effects.

**Reproductive Toxicity.** Recent epidemiological studies have suggested that exposure to radon and radon daughters during uranium mining may be associated with adverse reproductive outcomes (Dean 1981; Muller et al. 1967; Wiese and Skipper 1986). While the evidence of the possible reproductive effects of uranium mining is largely descriptive, reports of alterations in the secondary sex ratio among offspring of uranium miners merits further study. Currently there are no experimental data that evaluate the reproductive toxicity of radon and radon progeny exposure by any route. Controlled experiments that are designed to evaluate reproductive toxicity and that attempt to correlate the amount of alpha radiation to germ cells could provide an explanation of the effects that have been observed in the epidemiology studies.

**Developmental Toxicity.** Recent data indicate that mental retardation may result from low-level exposure of children to radiation during their development in utero (Otake and Schull 1984). While this effect may have resulted from external radiation rather than internally delivered radiation dose, the potential of ionizing radiation to induce developmental toxicity is generally accepted. No experimental data currently exist that evaluate the developmental toxicity of radon and radon progeny by any route. Controlled experiments that are designed to evaluate developmental toxicity and that attempt to correlate the amount of alpha radiation available to the fetus could show whether the effects observed following exposure to other forms of radiation also may occur following exposure to radon and progeny.

**Immunotoxicity.** No information currently exists on humans or laboratory animals regarding adverse effects on the immune system following exposure by any route to radon or radon progeny. However, data indicate that acute exposure to radon in laboratory animals results in a transient decrease in lymphocytes. Although these effects were transient, it is possible that the immune system may be compromised during this time. In addition, some epidemiological studies have reported increased chromosomal abnormalities

following exposure to radon and radon daughters. Depending upon the target cells in which these chromosomal changes occurred, adverse effects on the immune system could result. A battery of immunological tests administered to members of a nonminer cohort, such as radon spa workers or people exposed to high background levels, is needed to clarify whether immunological effects occur following exposure to radon or radon progeny. Animal studies designed to evaluate immune competence also are necessary to provide information on subtle alterations in immune function. In addition, lymphocytes and lymphatic tissues are sensitive to the radiation-induced damage caused by other alphaemitting radionuclides (ATSDR 1990b). Although lymphocytopenia observed in dogs exposed to plutonium is not seen following exposure to radon and radon daughters or uranium ore dust, other tests for immunocompetence have not been conducted (ATSDR 1990a, 1990b).

**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 which 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.** Epidemiological studies of uranium and hardrock miner cohorts in the United States, Czechoslovakia, and Canada have demonstrated an increase in lung cancer deaths. A similar increase in lung cancer deaths also has been reported in epidemiological studies of iron ore, zinc-lead, tin, phosphate, niobium, and fluorspar miners. Many of the persons included in the various mining cohorts began work in underground mines prior to 1969 when recommendations for the maximum radon daughter levels were established in United States mines or prior to 1972 when yearly exposure levels (4 WLM) for United States miners were proposed (MSHA 1989). (The WLM represents a cumulative exposure; see Section 2.1, Introduction or Appendix B.) Since institution of these guidelines, radon daughter levels in United States mines have decreased. For example, the average radon and radon daughter levels in United States uranium mines were as high as 10,000 pCi/L of air ($3.7 \times 10^5$ Bq/m$^3$) in the early 1950s but dropped to less than 100 pCi radon-222/L of air ($3.7 \times 10^2$ Bq/m$^3$) by 1968 (Lundin et al. 1971). Among the Colorado uranium miner study group, only a relatively small number of persons who have been exposed to low levels of radiation have had a long follow-up (Archer 1980). A continuation of the follow-up on this group is needed to contribute to the evaluation of health hazards at levels at or below the current exposure standard for radon daughters or at the levels present in the environment. Continuation of the follow-up of epidemiological studies of New Mexico uranium miners is also necessary because smoking is less frequent in this group than in other groups studied. Continuation of studies of underground miners exposed to radon daughters to cover the full lifetimes of the cohort members would generate useful information. Additional information on the smoking habits of these cohorts is required to provide some

insights on the complex interaction between radon daughters and cigarette smoking with regard to the induction of lung cancer. If exposure warrants, new population studies could be initiated or additional information could be gathered on previously defined populations.

The exact duration and level of exposure in human studies involving underground miners are not adequately characterized. Generally, approximate exposure is used based on environmental measurements of radon and radon daughters in the mines and individual work histories. The relationship between WLM and dose to the respiratory tract can differ in the occupational and environmental settings primarily due to differences in type and quantity of dust levels or ventilation rates. Additional evaluation of radon daughter dosimetry in various settings is needed to provide a better basis for estimating adverse health effects and correlating these effects with environmental exposures.

As with some of the chronic animal studies, exposures in most of the occupational miner cohorts consist of exposure to radon and radon progeny in the presence of other contaminants such as uranium ore dust, diesel-engine exhaust, or other mine pollutants. Only a few studies of lung cancer associated with environmental exposures to radon and radon daughters have been reported. These studies are primarily case-control or case-referent studies that involve a small number of subjects and have exposure estimates that are based on either surrogates for measurements or limited measurements. Additional studies of the extent of the hazard associated with environmental radon daughter exposures would provide useful information since radon is an ubiquitous substance, especially as they compare to estimates of the human health hazard based on the occupational setting.

**Biomarkers of Exposure and Effect**. 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 an ubiquitous substance and background levels of radon and radon progeny are needed to quantify higher than "average" exposures. It has been reported (Brandom et al. 1978; Pohl Ruling et al. 1976) that chromosome aberrations in the peripheral blood lymphocytes may be a biological doseresponse 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.** Some quantitative information is available on the absorption, distribution, and excretion of radon and radon daughters following inhalation and oral exposure, but information following dermal exposure is inadequate. Additional information

on the deposition patterns in airways for radon daughters and the relationship of these deposition patterns to the onset of respiratory disease is needed to enhance understanding of the disease process and delineate health protective measures to reduce deposition. In particular, further study of the role of ultra fine particles on lung doses is needed. More information on chronic exposure to low levels of radon in air and water is also necessary since this is the most common type of exposure for the majority of people who are exposed environmentally. Although absorption of radon via the oral route is known to occur, dosimetry of the gastrointestinal tract wall and the radiosensitivity of the wall is poorly understood. This information would be important in assessing the impact of oral exposure. Information on the storage of radon and radon daughters in fat tissue, especially following chronic exposure, is necessary to determine whether steady-state conditions can be achieved and the possibility of long-term bioaccumulation of radon daughters in body tissues. No information is available on the rate or extent of bioaccumulation of the long-lived radon daughter products such as lead-210 or polonium-210. This information is needed so that past exposures to radon may be quantified.

**Comparative Toxicokinetics.** Very little information is known about the comparative toxicokinetics of radon and radon daughters among animals and humans. However, 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 radon daughters 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 are needed to compare different routes of exposure.

### 2.8.3 On-going Studies

In recent years, concern over exposure to radon in both occupational and residential settings has increased. Consequently, numerous institutions have become involved in radon-related activities, partly to investigate the adverse health effects of radon. The following discussion is intended to be a representative sample of on-going research and is not an exhaustive list of the work in this area.

Several epidemiological studies pertaining to radon in homes and lung cancer incidence are underway. Comprehensive case-control studies of lung cancer among nonsmoking women are under investigation by M. Alavanja (NCI) in Missouri, Z. Hrubec (NCI) in Stockholm, Sweden, and New Jersey, J. Boice (NCI)

in Shenyang, China, J.H. Stebbings (Argonne National Laboratory), and G.W. Collman (National Institute of Environmental Health Sciences). All studies involve residential exposure to radon. Epidemiological studies of New Mexico uranium miners and tin miners are being conducted by J.M. Samet (University of New Mexico School of Medicine) and J.H. Lubin (NCI), respectively. C. Eheman (Centers for Disease Control) has been working with the National Park Service in assessing past and current radon exposure of employees who work in caves for the possibility of an epidemiology study of park service employees exposed to radon at home and in caves.

F.T. Cross (Pacific Northwest Laboratories) is studying the exposure-rate effect in radon daughter-induced carcinogenesis, and the role of oncogenes and the involvement of growth factors and receptors in radon-induced carcinogenesis. Similar studies on the influence of dose and dose-rate on carcinogenesis and other biological effects are being conducted by M. Terzaghi-Howe (Oak Ridge National Laboratories). F.T. Cross (Pacific Northwest Laboratories) is also continuing a series of animal experiments, in particular studies in rats with exposure to low cumulative doses of radon (more than 20 WLM). R.S. Caswell (National Institute for Standards and Technology) is developing a mechanistic model of the interaction of the alpha particles of radon and its daughters with the cells at risk in the lung.

L.A. Braby (Pacific Northwest Laboratories) is studying the malignant transformation of mammalian cells exposed to alpha particles that pass through the cell nuclei in an attempt to elucidate the mechanisms of action of radiation. The mechanisms of cell killing by alpha particles (M. Raju, Los Alamos Laboratories), cell neoplastic transformation from alpha particles (S.B. Curtis, Lawrence Berkeley Laboratory), and pulmonary tissue injury from radon/radon daughter exposure (T.M. Seed, Argonne National Laboratory) are also under investigation.

Radon-induced genotoxicity is another subject of interest under investigation. D.J. Chen (Los Alamos National Laboratories) is investigating the mechanistic basis for gene mutation induced by ionizing radiation in normal human fibroblasts. J.E. Turner (Oak Ridge National Laboratories) is examining the early physical and chemical changes produced by energetic alpha particles to elucidate the mechanisms involved in DNA damage. F.T. Cross (Pacific Northwest Laboratories) is studying the effects of exposure to radon on DNA and DNA-repair processes. M.N. Cornforth (Los Alamos National Laboratory) is attempting to provide quantitative data concerning both doseresponse and repairability of cytogenetic damage to human cells caused by ultra low doses of ionizing radiation. The types and yields of damage produced in mammalian-cell DNA by radon (J.F. Ward, University of California, La Jolla); radon-induced mutation in mammalian cells, utilizing a recombinant shuttle plasmid containing a target gene (S. Mitra, Oak Ridge National Laboratories); and cytotoxic, mutagenic, and molecular lesions induced in mammalian cells differing in DNA repair capabilities by low rates of radon and radon daughters (H.H. Evans, Case Western Reserve University) are under investigation. The direct effect of radon progeny and other high-LET alpha

radiation on DNA damage in respiratory epithelial cells (D.G. Thomassen, Lovelace Inhalation Toxicology Research Institute) and the biological consequences of high-LET alphas from radon on chromosomal and episomal DNA in human cells (J.E. Cleaver, University of California, San Francisco) are under investigation. Alteration in the DNA content of critical cells in the respiratory tract following exposure to radon and other aspects of radiationinduced damage to DNA is the current topic of study by many other investigators, such as N.F. Johnson (Lovelace Inhalation Toxicology Research Institute) and J.L. Schwarz (University of Chicago Medical Center).

Interaction of radon and radon progeny with other pollutants is another area of investigation. J.M. Daisey (University of California, Berkeley) and Y-S. Cheng (Los Alamos National Laboratories) are independently studying the complex interactions between radon and its progeny with other gaseous indoor pollutants. Further, F.J. Burns (New York University Medical Center) also is conducting experiments on rats to study lung cancer risk from inhalation of radon alone or in combination with other pollutants commonly found in the home environment. Interaction of radon and cigarette smoke in causing lung tumors in rats is being studied by S.H. Moolgavkar (Fred Hutchinson Cancer Research Center). The induction/promotion relationships associated with radon and cigarette smoke mixtures also are being studied by F.T. Cross (Pacific Northwest Laboratories).

Another factor that influences radon toxicity is the toxicokinetics of radon and radon progeny. Target regions of the lung for inhaled radon and radon progeny are being studied independently by R.R. Mercer (Duke University) and R.G. Cuddihy (Lovelace Inhalation Toxicology Institute) to determine the sensitivity of cell types located in the target regions. H-C. Yeh (Lovelace Inhalation Toxicology Research Institute) is quantifying radon deposition in the respiratory tract of humans, based on the mode of breathing, body size, and aerosol characteristics. B.S. Cohen (New York University Medical Center) is also conducting a similar study on humans and laboratory animals. A comparative morphometric study between dogs and humans is being conducted by E.S. Robbins (New York University Medical Center). W. Castleman, Jr. (Pennsylvania State University) is investigating the chemical and physical processes associated with radon distribution and effects. This would aid in assessing the mechanisms governing distribution, fate, and pathways of entry into biological systems. More studies related to the above topics are in progress by R.G. Cuddihy (Lovelace Inhalation Toxicology Research Institute), D.R. Fisher (Pacific Northwest Laboratory), N.H. Harley (New York University Medical Center), and D.L. Swift (Johns Hopkins University).