# 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 radium. Its purpose is to present levels of significant exposure for radium 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 an overall perspective of the toxicology of radium and a depiction of significant exposure levels associated with various adverse health effects.

It is important to note that in the various studies reviewed in the preparation of this document, dose levels have been presented by those authors in several ways. In order to facilitate comparisons among studies, these levels have generally been converted to an equivalent dose in microcuries ($\mu$Ci) and kilo-Becquerels (kBq). The historical definition of one curie is the disintegration rate exhibited by one gram of radium. There are 0.027 $\mu$Ci per kBq. In this document, comparisons are usually made between total administered amounts of radioactivity, in $\mu$Ci/kg and kBq/kg, instead of using a daily dosage level.

In the case of radium, as well as any radionuclide, it is important to note that, in addition to the usual routes of exposure that must be considered (inhalation, oral, dermal, and occasionally parenteral) for toxic chemicals, there is also external and internal exposure to emissions of alpha and beta particles and gamma rays; and it is these radioactive emissions which are considered to be responsible for most of the biologically deleterious effects observed in exposed persons. Further information about radionuclides is presented in Appendix B.

## 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.

### 2.2.1 Inhalation Exposure

Early workers using radium undoubtedly inhaled microscopic particles of the salts of radium as well as the daughter products resulting from their decay, as they worked with these compounds.

Therefore, they must have been continually exposed to alpha and beta particles as well as to the intense penetrating gamma radiation emitted by radium and its daughter products, including radon. Thus, any resulting health effects cannot be attributed to a specific cause but were probably the consequence of a combination of all the radiation insults to that individual.

#### 2.2.1.1 Death

No information has been located regarding the lethal effects of acute exposure to radium via inhalation.

An early case study described a 36-year-old chemist who had worked with radium for 14 years and then suddenly developed acute leukopenia and died of bronchopneumonia within a month after the onset (Reitter and Martland 1926). Autopsy data indicated that 14 PCi of radioactive material, including radium and mesothorium (radium-228), was found in the body, but the observation that 1 µci was found in the lungs (as compared with other internal organs such as the liver, gastrointestinal tract, heart, and kidneys which had no measurable levels of radioactivity) convinced the authors that inhalation was the primary route by which radium had entered the body. Most of the radioactivity was found in the skeleton.

No studies were located regarding lethality in animals after inhalation exposure to radium.

#### 2.2.1.2 Systemic Effects

No studies were located regarding systemic effects in humans or animals after inhalation exposure to radium.

#### 2.2.1.3 Immunological Effects

Acute leukopenia, with almost total absence of granular leukocytes, leukoblastic groups and lymphoid tissue in the bone marrow, was reported in the case of a 36-year-old chemist who had worked with radium for 14 years (Reitter and Martland 1926).

No studies were located regarding the following health effects in humans or animals after inhalation exposure to radium:

#### 2.2.1.4 Neurological Effects

#### 2.2.1.5 Developmental Effects

#### 2.2.1.6 Reproductive Effects

**2.2.1.7 Genotoxic Effects**

**2.2.1.8 Cancer**

**2.2.2 Oral Exposure**

It is important to note that effects observed after the ingestion of radium may be attributed not only to radium itself, but to the presence of any or all of its daughter products produced in vivo and their radioactive emissions.

**2.2.2.1 Death**

There is no information on the lethal effects of radium due to acute oral exposure. Many deaths, especially from bone cancer, have occurred in humans following long-term oral exposure to radium-226 and radium-228. As described by Rowland et al. (1978), female radium dial painters in the 1920s who "tipped" their paint brushes with their lips or tongues ingested radium in the process. The dial paint usually contained long-lived radium-226 and shorter-lived radium-228. A toxicity ratio has been developed for these isotopes; it has been estimated that radium-228 is about 2.5 times as effective, per μCi, in inducing bone sarcomas as radium-226 (Lloyd et al. 1986; Rowland et al. 1978; Rundo et al. 1986). For various other effects, estimates of the effectiveness of radium-228 relative to radium-226 have ranged from zero to six (Rundo et al. 1986). Estimated systemic intakes for these workers and other exposed persons are listed in the Argonne National Laboratory case tables (Gustafson and Stehney 1985). These estimates are extrapolations based on body radium content at the time of examination (whether from living subjects or exhumed remains), modified by the Norris retention function (Norris et al. 1955) to account for the decrease in body radium content since exposure, and the known or presumed ratios of these isotopes in the materials to which these persons were exposed (Rundo et al. 1986). Radium dose levels have been expressed as: effective systemic radium intake = (μCi radium-226) + 2.5 x (μCi radium-228).

Some of the radium dial painters ingested amounts of radium sufficient to cause death within a few years of their employment. Martland (1931) described the cases of 18 dial painters who died of cancer at ages 20 to 54 years old. Causes of death were listed as anemia, necrosis of the jaw, and osteogenic sarcoma. The typical period of exposure was about two years.

Radium was also used as a "rejuvenating" tonic in the 1920s and was available to the general public in bottled water. Gettler and Norris (1933) described a case of a 52-year-old man who drank about 1,400 bottles of "Radithor", containing radium at 2 μg/60 ml bottle, over a

5-year period (total dose: approximately 2,800 μCi or 56 μCi/kg or 2,074 kBq/kg for a 50-kg man). The cause of death was stated to be a combination of necrosis of the jaw, abscess of the brain, secondary anemia and terminal bronchopneumonia. However, it is important to note that each of these effects can also be attributed to other etiologies.

No studies were located regarding lethality in animals after oral exposure to any of the isotopes of radium.

**2.2.2.2 Systemic Effects**

Based on case studies of radium dial painters, Martland (1931) stated that anemia, regenerative anemia, aregenerative anemia, or pernicious anemia was listed on the death certificates of ten of 18 persons autopsied as part of this study. The bases of these diagnoses (e.g., clinical impressions of the cadaver, laboratory findings, etc.) were not clearly stated. Sharpe (1974) analyzed detailed hematological data relating to dial painters as well as to persons exposed to radium in other ways (eg., male laborers and equipment operators in radiumrelated industries). He concluded, however, that there were no consistent differences in hematological indices between the radiumexposed patients and closely matched controls. From the limited available data, it is difficult to determine if hematological effects are a concern for humans exposed to radium.

No studies were located regarding hematological effects in animals after oral exposure to radium.

No studies were located regarding the following health effects in humans or animals following oral exposure to radium.

**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**

**2.2.2.8 Cancer**

The Center for Human Radiobiology at the Argonne National Laboratory has been conducting a surveillance program to identify persons exposed to radium and to determine the details of their exposure, in some cases through exhumation of their remains (Gustafson and Stehney 1985). Based on their findings, bone sarcomas, carcinomas

of the perinasal sinuses and mastoid air cells (often called head cancers), and deterioration of skeletal tissue are considered to be the only effects that are unequivocally attributable to internal radium (Rundo et al. 1986).

These bone sarcomas and head carcinomas have been seen in many radium dial painters and have appeared from 5 to more than 50 years after first exposure to radium. Of those dial painters for whom radium intakes have been estimated (a total of 1,907), 41 have developed bone sarcomas, 16 developed head carcinomas, and an additional 3 cases developed both types. Among dial painters whose radium intakes were not estimated (a total of 2,928), 20 cases with bone sarcomas and 5 with head carcinomas were identified. Thus 85 out of 4,835 known dial painters developed a malignancy as a consequence of their oral ingestion of radium (Rundo et al. 1986).

Based on data on these dial painters from the 1985 listing of radium cases studied at the Argonne National Laboratory (Gustafson and Stehney 1985) Rundo et al. (1986) have estimated that the lowest total intake level of radium associated with a malignancy was 60 μCi (2,222 kBq) or 1.03 μCi/kg (38 kBq/kg) based on an estimated 58 kg body weight for a woman. These estimates are based on current radium body content modified by the Norris retention function (to account for the decrease in body radium content with time since exposure) and an estimate of radium-228 from measurements of radium-226 and the known or presumed ratios of these isotopes in the materials to which these persons were exposed (Rundo et al. 1986).

Osteogenic sarcomas were reported in 3 out of 5 rats administered radium for 20 days by dropper (Evans et al. 1944). Each animal was given a different estimated total dose ranging from 10 to 70 μCi. The lowest dose to clearly induce a malignancy was 22 μCi (approximately 73 μCi/kg or 2,703 kBq/kg).

### 2.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to radium.
It is important to note, however, that the radium dial painters had chronic dermal exposure to radium on their lips and tongues. Although no recognition of this fact has been located in the literature, it is noteworthy that no local effects on exposed skin have been described in the available case studies of these workers (eg., Martland 1931; Sharpe 1974).

#### 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**

**2.2.4 Other Routes of Exposure**

While parenteral exposure is not a route posing a significant environmental threat to human health from the isotopes of radium, data acquired in studies using this route are presented here because thousands of persons did acquire radium via this route, and most of the toxicity and metabolic studies with experimental animals have used this route. It is again important to note that effects observed after parenteral administration of radium may be attributed not only to radium itself, but to the presence of any or all of its daughter products and their radioactive emissions in vivo.

In the years after World War II (1946 to 1950), repeated injections of radium-224 were given to adults and children in Germany for treatment of tuberculosis, ankylosing spondylitis, and other diseases. Out of about 2,000 persons who received this treatment, 816 of these cases are currently being followed (Spiess et al. 1978). Of the 816, 204 were injected as juveniles (ages 1 to 20 years) and 612 as adults. The average total injected activity was 18 μCi/kg (666 kBq/kg) (Mays et al. 1985a).

A second study of persons injected with radium-224 in Germany from 1948 to 1975 included 1,473 ankylosing spondylitis patients who were also treated with repeated intravenous injections of radium, but at lower levels. They typically received a series of 10 to 12 injections at weekly intervals, each containing 28 μCi (1,037 kBq). Some patients received two or three such series, and one patient received four. The average total injected activity was 4.8 μCi/kg (178 kBq/kg) (Wick and Gossner 1983, 1989).

Pure radium-226 was given intravenously as a medication in the United States from the time it first became available until the mid-1930s. Treatment of patients at the Elgin State Hospital in Illinois was described by Schlundt et al. (1933), where from 1931 to 1933,

32 patients were given 10 μCi (370 kBq) injections, usually weekly, for periods ranging from about 2 to 6 months. In the 195Os, these patients were located, their radium body content was measured, and their health status was subsequently followed (Norris et al. 1955).

### 2.2.4.1 Death

No studies were located regarding acute lethality in humans following parenteral administration of radium isotopes. Early uses of radium-226 by physicians (usually as a treatment for arthritis) involved intravenous injections as large as 1 mg (1,000 μCi or 37,037 kBq) of elemental radium (thus approximately 14 μCi /kg or 518 kBq/kg), which were claimed to have no ill effects (Proescher 1914). As described in Section 2.2.4.8, patients receiving injections of radium have developed cancer which has resulted in death.

Injection of mice with radium (presumably radium-226) at 2,000 to 4,000 μCi/kg (74,000 to 148,000 kBq/kg) was fatal in 7 to 10 days (Proescher and Almquest 1914); however, experimental details were not provided. In 12-week-old mice given a single intraperitoneal injection of radium-224 or a series of 8 such injections over a period of 4 weeks, there was no evidence of a decrease in life span at any level, up to the maximum tested, approximately 60 μCi /kg (2,220 kBq/kg) (Humphreys et al. 1985).

### 2.2.4.2 Systemic Effects

No studies have been located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, renal, or dermal effects in humans or animals after parenteral administration of radium.

**Hematological Effects.** In a follow-up study of the second group of German patients who had received repeated intravenous injections of radium-224, the injected doses averaged 4.8 μCi/kg (178 kBq/kg) total exposure (Wick and Gossner 1983; Wick et al. 1986) for 1,501 patients. Ten cases of bone marrow failure were observed in these patients, as compared with 7 cases in the controls (1,338 similar patients not treated with radiation) (Wick and Gossner 1989). The statistical significance of these findings was not addressed.

In the bone marrow of mice given intraperitoneal injections of radium-226 at 17,820 μCi/kg (660,000 kBq/kg), there was a depression in the number of hemopoietic stem cells which lasted until at least 100 days after the injection but returned to normal by 300 days (Schoeters and Vanderborght 1981). Schoeters et al. (1983) reported a marked depression in the number of peripheral white blood cells of mice at 400 days after a 670 μCi (24,800 kBq) intraperitoneal injection of

the chloride salt of radium-226 (approximately 22,320 μCi /kg or 827,000 kBq/kg). At 530 days post-injection, these levels appeared to be recovering. There were no consistent trends in the peripheral white blood cell levels of the lower dose groups (3,960 and 10,000 μCi/kg or 147,000 and 370,000 kBq/kg).

**Hepatic Effects.** Chronic liver diseases, mostly cirrhosis, were reported in 20 cases (out of 682 adults and 218 children) who were followed for an average of 20 years after repeated injections of radium-224 totaling an average of 18 μCi/kg (667 kBq/kg). Eighteen of these patients were injected as adult men, one as an adult woman, and one as a juvenile. The authors suggested that this is a radiation effect; however, statistical significance was not addressed and the total incidence in this group (2.2%) may have been comparable to that of the general population. The higher incidence in men was thought to be related to their higher exposure to liver toxins such as alcohol or industrial chemicals (Spiess and Mays 1979).

**Ocular Effects.** Cataracts were reported in 6% (12/218) of patients injected with radium-224 as children. The known dosages averaged 28 μCi/kg (1,037 kBq/kg). Of these cases with known doses, 14% (11/80) had cataracts after receiving more than 28 μCi/kg (1,037 kBq/kg), whereas only 0.8% (l/131) developed cataracts after receiving less than that dose (Stefani et al. 1985). The younger patients received the highest doses in μCi/kg in this study, and thus, presumably, the highest radiation dose to the eye. The lowest dose known to be associated with a cataract that developed after a radium-224 treatment in childhood was 15.6 μCi/kg (577 kBq/kg) given to a 4.5 year-old-girl (Chmelevsky et al. 1988a).

In beagle dogs, intravenously injected radium-226 was deposited in the melanin granules of pigmented cells and rodlike organelles of the tapetum in the eye (a structure that humans do not have). Retention in the eye varied inversely with dose. At doses from 0.062 to 1.1 μCi/kg (2.3 to 41 kBq/kg), 1oss of pigment at the higher doses and melanosis and intraocular melanoma formation at the lower doses were observed (Taylor et al. 1972).

**Other Systemic Effects.** Radiation damage to dental tissue, or perhaps to its blood supply, initiates extensive resorption of the dentine, especially at the gum line. These radiation-induced caries weaken teeth and cause them to fracture easily. Such tooth breakage has been reported in 12% (27/218) of patients injected with radium-224 as children (20 years old and younger) and by 2% (17/681) of patients injected as adults (21 years old and older). The highest incidence

occurred in adolescents injected at 16 to 20 years of age (15/61 or 25%). Combining results from all age groups, the incidence of tooth fracture increased significantly with dose (p=0.01) (Sonnabend et al. 1986).

### 2.2.4.3 Immunological Effects

No studies were located regarding immunological effects in humans after parenteral exposure to radium.

A marked decrease was found in the number of peripheral white blood cells of mice at 400 days after an intraperitoneal injection of the chloride salt of radium-226 at about 22,320 μCi/kg (827,000 kBq/kg) (Schoeters et al. 1983). These results suggest that compromised immune function may be a concern for humans exposed to radium.

### 2.2.4.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after parenteral exposure to radium.

### 2.2.4.5 Developmental Effects

In a follow-up study of the first group of German patients injected with radium-224 as therapy for tuberculosis when they were children (see Section 2.2.4), it was found that the adult heights of these persons were markedly lower than the heights of nontreated persons. This effect was attributed to the formation of overcalcified "growth arrest plates" during the radium-224 injections. The reduction was greatest for those individuals who were the youngest at the age of injection; however, the youngest children were given the highest doses of injected radium-224 in μCi/kg (Spiess et al. 1985). The authors could not determine if this effect has a threshold but stated that the continued slowing of the growth rate long after irradiation suggests that some growth retardation may occur at very low doses of radium.

### 2.2.4.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following parenteral exposure to radium.

### 2.2.4.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following parenteral exposure to radium.

### 2.2.4.8 Cancer

Bone tumors, primarily osteogenic sarcomas, have appeared in the first group of German patients injected with radium-224 (see Section 2.2.4) (Spiess et al. 1989). A total of 56 sarcomas have been found; the expected number is 0.2 to 0.3 (Spiess et al. 1989). The lowest total dose associated with a bone tumor was 6.4 μCi/kg (237 kBq/kg) given over two months (Mays and Spiess 1984).

An elevated incidence of breast cancer has also been observed in the female patients in this group (14 cases versus 4.1 to 6.1 expected). Eight of these cases occurred among those injected as children, whereas only 0.6 to 0.9 were expected. In patients injected as adults, the 6 observed cases are not significantly different from the 3.5 to 5.2 cases expected (Spiess et al. 1989). This suggests that exposure to radium-224 during childhood poses a much greater risk for the induction of breast tumors than does exposure as an adult.

An elevated incidence of liver cancer has been seen in the first series of German patients (6 versus 1.1 to 1.2 expected). Five cases of kidney cancer have also been observed, compared with 2.4 to 2.6 expected (Spiess et al. 1989); however, this increase is not statistically significant. The authors suggest that these cancers may also have been induced by the radium-224.

In the second group of German patients treated with radium-224 (see Section 2.2.4), at lower injected doses, three malignant tumors in the skeleton have been observed (versus 0.4 to 0.7 expected); two were tumors of the bone marrow (a reticulum cell sarcoma and a plasmocytoma) and one was a fibrosarcoma (Wick and Gossner 1989). One skeletal tumor, a plasmocytoma, was observed among the controls, a group of 1,338 ankylosing spondylitis patients who were not treated with radiation (Wick and Gossner 1989).

Of the Elgin State Hospital patients who received injections of radium-226 (see Section 2.2.4), two patients developed bone sarcomas, four developed head carcinomas, and a seventh patient had both types of malignancy (statistical significance was not addressed) (Gustafson and Stehney 1985).

Large experimental animal studies with parenterally administered radium, primarily using dogs, but some using rats and mice, have demonstrated that radium-224, radium-226, and radium-228 can induce bone cancers and leukemias in these species (Evans et al. 1944; Humphreys et al. 1985; Kofranek et al. 1985; Mays et al. 1987; Taylor et al. 1983). However, head carcinomas, such as those found in humans, were not found in any of the species tested, indicating that this malignancy was not induced under the conditions of these animal studies. The most

unexpected finding was the induction of intraocular melanomas in beagles by radium-226 by Taylor et al. (1972). These tumors have not been seen in any of the human studies.

## 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 per unit mass and is expressed in rads (grays). Estimation of this radiation dose is sometimes accomplished by modeling the sequence of events involved in the acquisition, deposition, clearance, and decay of radium within the body. While based on the current understanding of experimental data on radium 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 BEIR IV (1988), ICRP (1979), and Raabe et al. (1983). In this section, the toxicokinetics of radium are described based on the available experimental data rather than on descriptions derived from models.

### 2.3.1 Absorption

#### 2.3.1.1 Inhalation Exposure

The only study located on human absorption of radium after inhalation exposure involved the accidental rupture of capsules containing radium sulfate (presumed to be primarily radium-226), with the resultant brief exposure of several laboratory workers (Marinelli et al. 1953). Radium was deposited both in the lungs and the skeletons of these individuals, indicating that some of the radium absorbed by the lung had entered the systemic circulation, ultimately depositing in the bones. Some of the radium, however, may have been coughed up and then swallowed during the original exposure and then entered the systemic circulation after being absorbed by the gut. The average half-life of the decrease of gamma ray activity from the thorax was reported to be about 120 days. The possibility of dermal exposure and consequent absorption during this episode was not addressed.

No studies were located regarding the absorption of radium in animals after inhalation exposure.

#### 2.3.1.2 Oral Exposure

Based on a study of elderly human subjects (aged 63 to 83 years) who ingested mock radium dial paint containing $^{224}RaS_4$, Maletskos et al. (1966, 1969) have estimated that about 80% of the ingested radium was promptly excreted via the feces during the first 10 days, and about 20% was retained and distributed systemically. The feces to urine excretion

ratios remained high (about 30:1) during another phase of this study in which similar subjects were given intravenous injections of radium-224. This suggested that biliary excretion is probably involved and that perhaps more than the estimated 20% of ingested radium was actually absorbed. However, this topic was not addressed in the study.

Measurements of body radium acquired by adult and teenage males solely from natural levels of radium in food and water indicated that approximately twice the amount of ingested radium was retained by younger males from one location, Lockport, Illinois (mean age: 16.6 years) than by older males in a penitentiary in Stateville, Illinois (means of age groups: 27, 38 and 44 years) (Stehney and Lucas 1955). Among the prisoners, mean body radium content was increased with the mean age of the men. However, boys from another location, Chicago, Illinois (mean age: 16.6 years) had similar radium body contents to that of the single Chicago adult man participating in this study. The results of this study also suggested that the absorption of radium from water was greater than that from food, based on excretion rates measured in areas where either food or water was the predominant source of radium. The authors acknowledged that these were speculations and not clearly supportable by the results of their limited study.

In rats, the absorption of orally administered radium may be quite low. At 400 to 500 days after administration, they retained 1 to 7% of the ingested radium, primarily in the skeleton. In contrast, rats intradermally injected with radium retained 77% of the administered radium at 140 to 300 days after injection (Evans et al. 1944). Differences seen in the results of these two studies could reflect differences in time frame and/or the route of administration. The probable influence of biliary excretion of orally administered radium and the possibly slow rate of absorption of intradermally administered radium from the site of injection may help account for these differences.

#### 2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of radium in humans or animals after dermal exposure.

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

Based on the observations of Marinelli et al. (1953), immediately after accidental exposure of humans to radium-226 (as the sulfate), the major deposit of radium was in the lungs. This deposition decreased with an average half-life of 118 days (±30 days). Elimination from the lungs via the systemic circulation results in a continuous deposition in

the skeleton as well as distribution to soft tissue and the excretory system. In addition, some of the radium salt may have been coughed up and swallowed during the exposure episode.

It is assumed that radium that has been deposited in the lung as a radium salt enters the systemic circulation either as that salt or as individual radium atoms at a rate dependent upon the solubility and chemical characteristics of the specific radium salt involved. Subsequently, these salts or radium atoms would be systemically transported in the same manner as radium acquired by oral or parenteral administration. However, some of the radium in the lung could be retained for a long time before this process is completed. The ultimate distribution, many years after an inhalation exposure, would probably be very similar to that of other routes of administration; that is, most of the radium that was retained in the body would eventually be deposited in the skeleton (Marinelli et al. 1953).

**2.3.2.2 Oral Exposure**

No studies have been located that specifically follow the distribution of radium in humans or animals following oral exposure. Distribution to the skeleton is assumed due to the findings of osteosarcomas in the dial painter studies as well as the presence of radium in their exhumed skeletal remains. The affinity for bone is assumed to be related to its similarity to calcium (BIER IV 1988).

**2.3.2.3 Dermal Exposure**

No studies were located regarding the distribution of radium in humans or animals following dermal exposure.

**2.3.2.4 Other Routes of Exposure**

Parenteral administration of radium to humans results in short-term distribution to soft tissue which is rapidly followed by deposition of most of the radium in the skeleton (BEIR IV 1988).

Radium, similarly to calcium, deposits in bone within those areas where new bone mineral is being formed and also on all bone surfaces. Radium remains in those areas of new bone formation, but the radium deposits on bone surfaces eventually move into the depths of compact bone as new bone matrix is deposited on top of them. In this deposition process, short-lived radium-224 rapidly decays, leaving no radioactivity within bone; whereas, long-lived radium-226 remains in the skeleton indefinitely (Rowland 1966). Mays et al. (1975) have demonstrated that the radon to radium ratio in bone increased with time after injection in beagles.

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Injected radium is deposited in the eye of the dog (Taylor et al. 1972) and to some extent in the human eye (Chmelevsky et al. 1988a).

### 1.3.3 Metabolism

Radium is an element and cannot be metabolized. In biological systems in which radium salts are deposited, these compounds will dissociate based on their solubility in that media. Radioactive decay of the radium cation occurs over time.

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

Based on a study of persons exposed to radium-226 during an industrial accident which involved the rupture of a capsule containing the insoluble salt radium sulfate (Marinelli et al. 1953), the excretion of radium occurred in two phases. In the initial phase, 2 to 4% of the estimated total body burden was excreted in the urine over a few days and was attributed to the elimination of radium ingested during the incident (due to the coughing up and swallowing of ingested radium). (Fecal excretion was not monitored.) In the second phase, about 100 days after the exposure, the urinary excretion rate was higher than predicted from the authors calculations (based on retention/excretion models on dogs injected with radium chloride). This phase was attributed to the presence of more radium in circulation than expected as a consequence of a continual release of radium sulfate from the lung.

#### 2.3.4.2 Oral Exposure

Following oral exposure to radium, excretion occurs in two phases. In the first phase, approximately 80% of the ingested radium is rapidly eliminated through the feces. In the slower second phase, most of the 20% that was absorbed into systemic circulation, is ultimately excreted from the body via the feces (Maletskos et al. 1966, 1969). These observations suggest that biliary excretion is probably involved; however, no information has been located on that topic.

#### 2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of radium in humans or animals after dermal exposure.

#### 2.3.4.4 Other Routes of Exposure

Following intravenous administration of radium-224 to elderly human subjects (63 to 83 years), the excretion of radium was primarily via the feces, with fecal to urinary ratios of about 30-to-1 usually observed

(Maletskos et al. 1966, 1969). Although these observations suggest that biliary excretion is involved, no data are available to verify that assumption. The whole body retention was about 15% after 20 days.

The excretion of parenterally acquired radium from the human body occurs in two phases; the first phase is very rapid, but the small fraction that remains in the body is ultimately released very slowly, presumably due to the turnover of bone matrix. An equation to describe the retention of radium in the human body, derived by Norris et al. (1955), predicts that the retention of radium 10 days after acquisition will be 16%, dropping to 2.5% at 1 year, 0.76% at 10 years, and 0.43% at 30 years. A similar equation has been developed for dogs.

Seil et al. (1915) studied the excretion pattern of radium that had been subcutaneously injected as the chloride salt into two dogs. The resulting measurements varied widely over the next few days; however, it was clear that there was a rapid initial elimination of radium in the feces and that fecal to urinary excretion ratios were typically about 10-to-l.

In a study in dogs, it was shown that long-term retention of radium is dependent upon age at injection, with younger dogs (3 months old) that were still undergoing skeletal growth retaining more of the injected activity than older dogs (18 months to 2 years old). However, very young dogs (2 to 5 days old), undergoing major skeletal growth and changes in bone shape lost most of their injected radium in the course of these processes (Bruenger et al. 1983).

## 2.4 RELEVANCE TO PUBLIC HEALTH

**Death.** Death and decreased longevity have been reported in persons who have had long-term exposure (approximately one or more years) to radium. A 52-year-old man died following 5 years of consumption of about 1,400 bottles of water containing radium at 2 μg per bottle, resulting in the total ingestion of approximately 2,800 μCi or 56 μCi/kg (2,074 kBq/kg) for a 50-kg man (Gettler and Norris 1933). However, the causes of death (jaw necrosis, brain absess, secondary anemia, and bronchopneumonia) can also be attributed to other etiologies. Case studies of women who died following ingestion of radium in dial paint were reported by Martland (1931). Deaths were attributed to anemia, necrosis of the jaw, and osteogenic sarcomas. A typical exposure duration was about two years. A 36-year-old chemist who had worked with radium for 14 years died of bronchopneumonia (Reitter and Martland 1926). Autopsy results suggested to the authors that inhalation was the main route of radium intake.

## 2. HEALTH EFFECTS

No deaths of patients (being treated mostly for arthritis) were reported to result from intravenous injections of radium at amounts up to 1,000 μCi or 14 μCi/kg (518 kBq/kg) (Proescher 1914). However, these patients may not have been followed clinically for more than a few months after these injections.

Studies using mice have shown life-shortening effects of intravenously injected radium-226 at high dose levels (2,000 to 4,000 μCi/kg or 74,074 to 148,148 kBq/kg) (Proescher and Almquest 1914). Injection of mice with radium-224 at lower levels (up to 60 μCi/kg or 2,222 kBq/kg) did not result in life-shortening effects (Humphreys et al. 1985).

Based on the results in humans and animals, lethality is a major public health concern associated with long-term low-level or short-term high-level exposure to radium. As discussed previously, total cumulative intake appears to be the most important factor in relation to health effects related to radium exposure.

**Systemic Effects.** Diseases of the hematopoietic tissues have been reported in patients given repeated injections of radium-224. Anemia, panmyelophthisis, and chronic myeloid leukemia were seen in excess of the control levels in these cases (compared with a higher incidence of acute leukemia in the control group) (Wick et al. 1986). Anemia has also been reported in case studies of the radium dial painters (Martland 1931), but the disease patterns have not been clearly established (Sharpe 1974).

Studies with mice injected with radium-226 at 24 μCi/kg (889 kBq/kg) have demonstrated reductions in the hemopoietic stem cells of the bone marrow for at least 100 days after radium acquisition (Schoeters and Vanderborght 1981).

Ocular effects have not been reported in humans or animals exposed to radium via inhalation, oral, or dermal routes. However, ocular effects have been observed in both humans and animals injected with radium. Cataracts were reported in 6% of the German patients who had been injected with radium-224 as children (Chmelevsky et al. 1988a; Stefani et al. 1985). In contrast, the incidence of cataracts in female dial painters was not correlated with total radium intake or age at first exposure, nor was there a difference in appearance times between high and low total radium intakes (Adams et al. 1983). However, the dial painters were exposed orally, the isotope was mainly radium-226, and very few of these dial painters were exposed when younger than 15 years of age. Any of these factors may account for the difference between the results observed in these two studies.

## 2. HEALTH EFFECTS

In beagle dogs, intravenously injected radium-226 resulted in melanosis and intraocular melanoma formation at the lower doses and a loss of pigment at the higher doses (Taylor et al. 1972). In this study, deposition of radium was found in the melanin granules of pigmented cells and rodlike organelles of the tapetum of the eye (a structure that humans do not have). Although this process cannot take place in humans, these results further suggest that the eye may be a target for absorbed radium in exposed humans.

**Other Systemic Effects.** Information on other systemic effects is not available for humans or animals exposed to radium via inhalation, oral, or dermal exposure. However, tooth breakage has been reported to occur in the German patients who were injected with radium-224 (Sonnabend et al. 1986). The incidence of these dental fractures was highest (25%) in persons who had been injected at 16 to 20 years of age, as compared with 12% in the total group of persons injected at age 20 years and younger, and 2% in persons injected when they were 21 years old and older.

**Immunological Effects.** Evidence of radium's potential effects on the human immune system was presented by Reitter and Martland (1926) in the case study of a chemist who developed acute leukopenia after working with radium for 14 years. Autopsy revealed almost total absence of granular leukocytes, leukoblastic groups, and lymphoid tissue in the bone marrow. Similarly, Martland (1931) described the development of leukopenia in the radium dial painters.

**Schoeters et al.** (1983) showed a reduction in the number of peripheral white blood cells of mice at 400 days after an intraperitoneal injection of radium-226. These observations suggest that immunological effects may be an important area of concern for persons occupationally exposed to radium.

**Cancer.** In humans, radium-224 is known to induce bone sarcomas, and it is strongly suspected of inducing breast cancer in females who received this isotope when younger than 21 years of age at total doses greater than 12 μCi/kg (444 kBq/kg). Liver and kidney cancers are also possibly induced by radium-224 (Spiess et al. 1989).

Bone sarcomas are known to be induced by both radium-226 and radium-228, while carcinomas of the bones enclosing the mastoid air cells and paranasal sinuses are known to be induced by exposure to radium-226. These carcinomas are believed to be caused by radon, a gaseous daughter product of radium-226, which migrates from the location where it was formed and becomes trapped within air cells in these structures. Here the subsequent decay products of radon irradiate the sensitive cells on the surfaces, and this irradiation is thought to

induce the malignant change. Breast cancer and multiple myeloma were found to be elevated in female dial painters, but these effects may be the consequence of the external radiation from the radioactive paint that was used by these workers (Rowland et al. 1989; Stebbings et al. 1984).

In Great Britain, radium dial painters with higher total radium-226 intakes and who were younger than 30 years of age at the start of painting showed an excess of breast cancers (Baverstock and Papworth 1989). External gamma ray exposure to the radioactive paint could also have been the cause of cancer in this population.

In experimental animals, bone cancer has been the most prominent consequence of radium incorporation and has been found in all species tested.

It should be noted that leukemia, which is often induced in humans by irradiation of marrow cells, has not been observed to occur in excess in the studies of the radium-irradiated populations (i.e., dial painters; patients receiving intravenous injections) above the numbers expected for nonirradiated populations (Baverstock and Papworth 1985; Spiers et al. 1983; Spiess et al. 1989).

## 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 radium 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 epithelial 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 radium 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 Radium

Exposure to radium can be determined by use of a whole body counter to measure the presence of gamma radiation emitted by radium (Toohey et al. 1983). Radium levels can also be measured in urine, feces, and other biological media by means of gamma-ray spectroscopy (Lloyd et al. 1983).

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

Humans have not been shown to develop specific adverse effects as a result of exposure to radium. Osteogenic sarcoma and cataracts are associated with radium exposure but can also result from other causes. Similarly, chromosomal aberrations may result from radium exposure as well as from other factors such as cigarette smoking or occupational exposure to solvents.

Attempts to correlate the estimated total intake of radium with observed health effects, especially bone cancer, have been conducted at the Argonne National Laboratory (Gustafson and Stehney 1985). For example, Rundo et al. (1986) have estimated that the lowest total intake level of radium associated with a malignancy (bone sarcoma) was 60 μCi (2,222 kBq) or 1.03 μCi/kg (38 kBq/kg) based on an estimated 58-kg body

weight for a woman. If data associated with exposed populations were fully analyzed, levels of radium in human tissue might be a good predictor of at least the potential for developing bone cancer. However, there is expected to be some degree of uncertainty, as in cases of persons with high levels of exposure to radium (such as some of the dial painters, the case of the chemist described by Reitter and Martland and the man who drank 1,400 bottles of "Radithor"), who did not develop bone cancer (Gettler and Norris 1933; Martland 1931; Reitter and Martland 1926).

## 2.6 INTERACTIONS WITH OTHER CHEMICALS

No data have been located which evaluate the health effects of radium in any of its isotopic forms in combination with any other chemicals or radionuclides.

## 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

The available studies suggest that persons who are exposed to radium during childhood or adolescence may be at greater risk from the potential health effects of radium, especially tooth breakage (Section 2.2.4.2), reduction in bone growth (Section 2.2.4.5), and breast tumors (Section 2.2.4.8). There may also be a subpopulation of humans who are genetically more susceptible to the development of bone cancer (Floyd et al. 1983). Patients with Paget's disease have 10 to 100 times the risk of bone sarcoma than the general population.

## 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 radium 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 these health effects (and techniques for developing methods to determine such health effects) of radium.

The following categories of 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. HEALTH EFFECTS

## 2.8.1 Existing Information on the Health Effects of Radium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to radium are summarized in Figure 2-l. The purpose of this figure is to illustrate the existing information concerning the health effects of radium. 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-l indicates whether information on the endpoint of a particular health effect is available for a specific route and duration of exposure for radium. Some information was located concerning human inhalation or oral exposure to radium, and no information was located concerning effects following dermal exposure to radium by humans. The only information available for animals is an intermediate-duration study in rats conducted via the oral route that resulted in cancer. There is virtually no information on noncancer endpoints from animal studies. As discussed in previous sections, most available information on radium is the result of studies using parenteral administration.

In general, the adverse effects of radium are believed to be the consequence of the radiation emitted from the element itself and its daughter products. Because there is already a considerable amount of information on the effects of radiation on humans and animals deri-ved from studies on the effects of the atomic bomb and of therapeutic x-ray and gamma-ray treatments of malignancies, the experimental animal studies with radium have made no attempt to duplicate this information. They have instead concentrated on radium's most sensitive endpoint, cancer. For example, it can be predicted that the beta and gamma rays emitted by a radium source will produce local radiation burns and tissue damage when the source is placed on human or animal skin, hence there have been no valid reasons to conduct such studies with radium.

## 2.8.2 Identification of Data Needs

Acute-Duration Exposure. There is no information available on the effects of acute-duration exposure to radium by humans or animals via inhalation, oral, or dermal exposure. The available toxicokinetic data suggest that radium can be absorbed and retained after inhalation and oral exposure. Although there are some toxicokinetic data that provide information on the retention of inhaled radium sulfate in the lung, it is not clear whether this compound and other salts of radium would remain in the lung long enough after acute-duration exposure to cause local effects such as lung cancer or other carcinogenic or noncarcinogenic systemic effects.

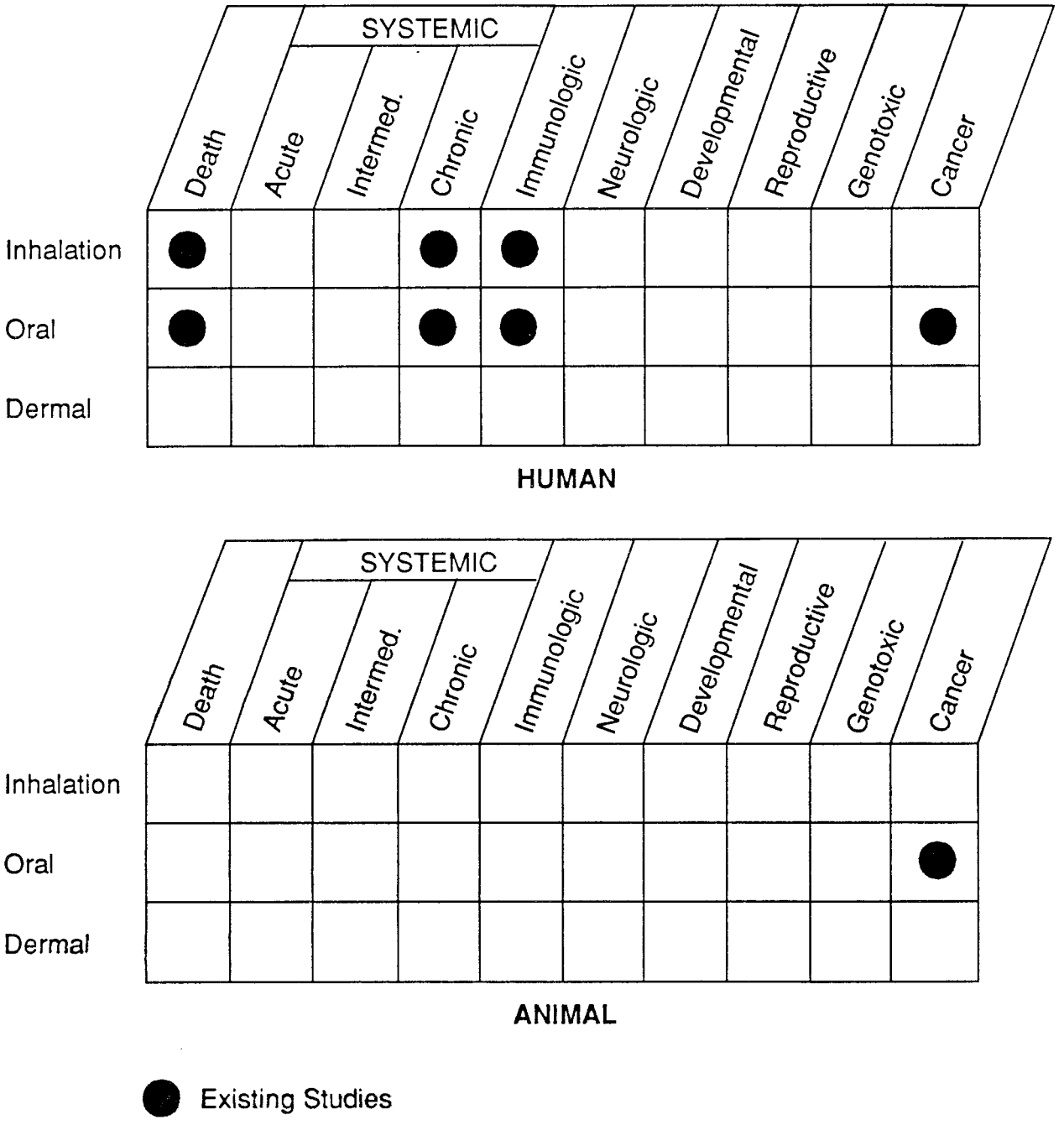


**FIGURE 2-1. Existing Information on Health Effects of Radium**

Animal studies conducted via the inhalation, oral, and dermal routes of exposure for this duration period would be useful since the potential short-term effects of such exposure as well as effects that could emerge years later, such as cancer, are not known.

**Intermediate-Duration Exposure.** There are no data on intermediate-duration exposure of humans to radium via the inhalation, oral, or dermal routes. There are no data on animals exposed via inhalation or the dermal route. The only information located was a very limited 20-day oral study in rats that resulted in osteogenic sarcomas. The data were not sufficient to calculate an MEL by any route. The available toxicokinetic data show that radium can be absorbed and retained after inhalation or oral exposure, although quantitative data are lacking. It would be useful to have information on the effects of intermediate-duration exposure to radium via inhalation, oral, and dermal routes in order to help assess the potential health effects of exposure to radium in the vicinity of hazardous waste sites and other settings, and to evaluate the possibility of long-range effects such as cancer that may emerge years later.

**Chronic-Duration Exposure and Cancer.** A case report is available on human chronic-duration exposure to radium via inhalation and indicates that acute leukopenia, bronchopneumonia, and death occurred in a chemist after 14 years of exposure. A case report is also available on a man who regularly consumed bottles of a "rejuvenating" tonic containing radium for about 5 years, resulting in effects described as necrosis of the jaw, abscess of the brain, secondary anemia, bronchopneumonia, and death. (Each of these causes of death can also be attributed to other etiologies.) Numerous studies have followed the dial painters who ingested radium, and effects reported in these studies include anemia, bone sarcomas, head carcinomas, and death. Although dermal exposure to radium also occurred in these cases, skin effects have not been reported. No data are available on chronic-duration exposure to radium by animals via any route of exposure. The available data were not considered to be adequate to calculate an MEL for any route of exposure. Animal studies on the noncarcinogenic effects of chronic-duration exposure to radium via inhalation, oral, and dermal exposure would be useful in assessing the potential health risks of humans chronically exposed to low levels of radium in the vicinity of hazardous waste sites and other settings.

Bone cancer has occurred in humans after chronic-duration oral exposure to radium and in rats that were orally exposed in an intermediate duration study (20 days). It would be useful to have carcinogenicity information from animal studies conducted via

inhalation, oral, and dermal exposure since humans in the vicinity of hazardous waste sites and other settings would be exposed to radium via all routes of exposure.

**Genotoxicity.** Neither in vitro nor in vivo genotoxicity studies have been located for radium. A battery of in vitro genotoxicity tests may provide useful information on the mechanism of carcinogenicity for radium.

**Reproductive Toxicity.** No studies were located on reproductive effects of radium in humans or animals via inhalation, oral, or dermal exposure. Animal studies using the oral route would be especially useful in evaluating the potential for these effects in human populations exposed to high levels of radium in drinking water (eg., more than 5 pCi). Studies using dermal and inhalation exposure would also be useful, since these are also probable routes of human exposure to radium in the vicinity of hazardous waste sites and other settings.

**Developmental Effects.** No information has been located on developmental effects in humans or animals resulting from inhalation, oral, or dermal exposure to radium. It was observed that radium-224 injected into young children markedly reduced their adult height due to radiation damage to the growth plate in the long bones. Animal studies via inhalation, oral, and dermal exposure would be useful in determining if radium, like calcium, can cross the placenta and enter fetal circulation, and can have adverse effects upon fetal development.

**Immunotoxicity.** Studies that assess the potential effects of radium on the immune system of orally or dermally exposed humans have not been located. The case report of a chemist exposed to radium primarily via inhalation for 14 years reported leukopenia and the almost total absence of granular leukocytes, leukoblastic groups, and lymphoid tissue in the bone marrow. No studies on animals exposed via inhalation, oral, or dermal routes have been located. A study reporting a reduction in peripheral white blood cells in intraperitoneally injected rats has been located. The reported observations suggest that immunological effects may be a concern for humans exposed to radium. A battery of immune function tests conducted in animals via inhalation and the oral and dermal routes would provide useful information relative to this concern.

**Neurotoxicity.** No reports of neurotoxicity resulting from inhalation, oral, or dermal exposure were located in the available human and animal studies. No further information appears to be needed at this time.

## 2. HEALTH EFFECTS

**Epidemiological and Human Dosimetry Studies.** Two large studies in Germany that follow radium-224 injected patients are being conducted by Spiess and by Wick and Gossner, and the radium study being conducted at Argonne National Laboratory has developed a large data base with information on the radium dial painters, patients who were medically treated with radium, and other persons exposed to radium. These studies will be of value in determining any effects that may be experienced by these aging populations. Additional data are not needed at this time.

**Biomarkers of Exposure and Effect.** Currently, human exposure to radium can be assessed by the presence of radioactivity in the body as measured by a whole body counter and in biological fluids such as blood or urine by gamma spectroscopy.

Effects specifically related to radium exposure have not been identified. Studies to identify potential biomarkers of radium's subtle effects would be useful as indicators that immediate mitigation of exposure to radium is warranted or that serious effects such as bone cancer may follow.

**Absorption, Distribution, Metabolism, and Excretion.** Quantitative data on the absorption of radium after intake via any exposure route are very limited. No data were located on the absorption of radium after dermal exposure. Information on laboratory workers exposed to radium during an industrial accident indicates that absorption can occur via the inhalation route. A study in elderly human subjects indicated that at least 20% of the ingested radium-224 in mock radium dial paint was absorbed and retained. No studies were located on the absorption of radium by animals after inhalation or dermal exposure. A study of orally exposed rats indicated that retention of radium at 400 to 500 days was 1% to 7% of the administered dose. Further studies to investigate the absorption and retention of radium after inhalation, oral, and dermal exposure would be helpful in elucidating the relative risks associated with exposure by each route.

No studies have been located regarding the distribution of radium in humans after oral or dermal exposure. Due to the findings of osteosarcomas in the radium dial painters and in a study in rats and the presence of radium in the exhumed skeletal remains of the dial workers, it is assumed to deposit in the bone after oral exposure. Data from a study of laboratory workers exposed via inhalation during an accident and a case report of a chemist exposed for 14 years also indicate that most radium was deposited in the skeleton. In the case of the chemist, no measurable levels of activity were found in the liver, gastrointestinal tract, heart, or kidneys. Information on radium

distribution following inhalation, oral and dermal exposure would be useful in helping to determine the potential target organs in persons exposed via each route.

Radium salts, such as radium sulfate, can be dissociated to $Ra^{2+}$ and the corresponding anion. However, radium is an element and cannot be metabolized. It is changed over time by the decay of its isotopic forms, each at its own rate. Therefore, no information is needed in this area.

Excretion data in orally and parenterally exposed humans indicate that feces is the major route of radium excretion and that biliary excretion is probably also involved. Some urinary elimination also takes place in persons exposed via inhalation, oral, and dermal routes. Continued excretion for months after exposure has been attributed to the release of radium from the lungs in persons exposed via inhalation and from the turnover of bone matrix in persons exposed orally or via parenteral administration. It would be useful to have quantitative information on the excretion patterns of radium administered to animals via inhalation, oral, and dermal administration and to more clearly elucidate the role of biliary excretion in the elimination process.

**Comparative Toxicokinetics.** There are currently not enough data to evaluate any potential species-related differences in response to radium exposure by any route. It would be useful to have information on which animal models most closely approximate humans in this regard in order to help interpret the relevance to humans of any toxicity findings in animal studies. Studies on the toxicokinetics of radium following inhalation, oral, and dermal exposure are needed to compare the different routes of exposure.

### 2.8.3 On-going Studies

In Germany, Spiess is following about 900 patients who were injected with radium-224 immediately after World War II. Wick and Gossner are following a larger group of about 1,500 patients injected more recently with lower doses of radium-224. These studies are currently active, and summaries of their data are published periodically.

The Center for Human Radiobiology at the Argonne National Laboratory is the repository for all data accumulated in the United States on radium-exposed persons. This study has recently been severely reduced in magnitude, but the records on 5784 cases remain available at the laboratory (Rundo et al. 1986).

## 2. HEALTH EFFECTS

Two large studies of radium and other bone-seeking radionuclides in dogs were conducted at the University of Utah (Wrenn et al. 1986) and at the University of California at Davis (Raabe et al. 1981, 1983). Results of both projects are still being analyzed.