2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

The health effects associated with oral or dermal exposure to natural and depleted uranium appear to be solely chemical in nature and not radiological, while those from inhalation exposure may also include a slight radiological component, especially if the exposure is protracted. A comprehensive review by the Committee on the Biological Effects of Ionizing Radiation (BEIR IV) concluded that ingesting food or water containing normal uranium concentrations will most likely not be carcinogenic or cause other health problems in most people. Inhaled uranium is associated with only a low cancer risk, with the main risk being associated with the co-inhalation of other toxic and/or carcinogenic agents, such as the radioactive transformation products of radon gas and cigarette smoke. Very high oral doses of uranium have caused renal damage in humans. Animal studies in a number of species and using a variety of compounds confirm that uranium is a nephrotoxin and that the most sensitive organ is the kidney. Hepatic and developmental effects have also been noted in some animal studies. This profile is primarily concerned with the effects of exposure to natural and depleted uranium, but does include limited discussion regarding enriched uranium, which is considered to be more of a radiological than a chemical hazard. Also, whenever the term “radiation” is used, it applies to ionizing radiation and not to non-ionizing radiation.

Although natural and depleted uranium are primarily chemical hazards, the next several paragraphs describe the radiological nature of the toxicologically-important uranium isotopes, because individual isotopes are addressed in some of the health effects studies. Uranium is a naturally occurring radioactive element and a member of the actinide series. Radioactive elements are those that undergo spontaneous transformation (decay), in which energy is released (emitted) either in the form of particles, such as alpha or beta particles, or electromagnetic radiation with energies sufficient to cause ionization, such as gamma or X-rays. This transformation or decay results in the formation of different 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 D for more information).

Uranium exists in several isotopic forms, all of which are radioactive. The most toxicologically important of the 22 currently recognized uranium isotopes are anthropogenic uranium-232 (^{232}U) and uranium-233 (^{233}U) and naturally occurring uranium-234 (^{234}U), uranium-235 (^{235}U), and uranium-238 (^{238}U). When an atom of any of these five isotopes decays, it emits an alpha particle (the nucleus of a helium atom) and transforms into a radioactive isotope of another element. The process continues through a series of radionuclides until reaching a stable, non-radioactive isotope of lead. The radionuclides in these transformation series (such as radium and radon), emit alpha, beta, and gamma radiations with energies and intensities that are unique to the individual radionuclide.

Natural uranium consists of isotopic mixtures of ^{234}U, ^{235}U, and ^{238}U. There are three kinds of mixtures (based on the percentage of the composition of the three isotopes): natural uranium, enriched uranium, and depleted uranium. Natural uranium, including uranium ore, is comprised of 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U by mass. Combining these mass percentages with the unique half-life of each isotope converts mass into radioactivity units and shows that uranium ore contains 48.9% ^{234}U, 2.25% ^{235}U, and 48.9% ^{238}U by radioactivity, and has a very low specific activity of 0.68 µCi/g (Parrington et al. 1996). Enriched and depleted uranium are the products of a process which increases (or enriches) the percentages of ^{234}U and ^{235}U in one portion of a uranium sample and decreases (or depletes) their percentages in the remaining portion. Enriched uranium is quantified by its ^{235}U percentage Uranium enrichment for nuclear energy produces uranium that typically contains 3% ^{235}U. Uranium enrichment for a number of other purposes, including nuclear weapons, can produce uranium that contains as much as 97.3% ^{235}U and has a higher specific activity (. 50 µCi/g). The residual uranium after the enrichment process is called “depleted uranium” (DU), which possesses even less radioactivity (0.36 µCi/g) than natural uranium. The Nuclear Regulatory Commission (NRC) considers the specific activity of depleted uranium to be 0.36 µCi/g (10 CFR 20), but more aggressive enrichment processes can drive this value slightly lower (0.33 µCi/g). In this profile, both natural and depleted uranium are referred to as "uranium." The higher specific-activity mixtures and isotopes are described in the profile as "enriched uranium," or as ^{232}U, ^{233}U, or ^{234}U, as applicable, in the summary of the studies in which these mixtures and isotopes were used.

Because uranium is a predominantly alpha-emitting radionuclide, there is a concern for potential DNA damage and fragmentation if alpha particles reach cell nuclei. Attempts by cells to repair this

fragmentation, if it occurs, may result in repair errors, producing gene mutations or chromosomal aberrations. These effects, when sufficiently severe, may be manifested as cancer and possibly as developmental malformations. However, the genetic effects of radiation have not been observed in humans with exposure to radiation, including that from uranium. Ionizing radiation may also promote carcinogenesis by an apoptotic mechanism by which radiation-induced cell death in tissues or organs elicits an increased cell proliferation response to replace the lost cells. Increased mitotic activity may afford cancer cells a preferential advantage in clonal expansion.

Although radiation exposure has been generally assumed to be carcinogenic at all dose levels, no correlation has been established at low doses such as occur from exposure to natural radiation background levels. This is largely attributable to two factors: (1) it is difficult to construct and obtain meaningful data from epidemiological studies where exposure is near background exposure levels, and (2) the data are not statistically significant enough to substantiate a detectable health impact. Recent risk assessment reviews of carcinogenicity and exposure to hazardous chemicals, including radiation, have been questioning the non-threshold assumption. With specific reference to radiation, there is increasing biological evidence that there is a threshold for radiation-induced carcinogenicity (Clark 1999).

The National Research Council Committee on the Biological Effects of Ionizing Radiation BEIR IV report stated that ingesting uranium in food and water at the naturally occurring levels will not cause cancer or other health problems in people. However, based on the zero-threshold linear dose-response model (a conservative model that is inherently unverifiable and is intended to be used as an aid to risk-benefit analysis and not for predicting cancer deaths), the BEIR IV committee calculated that the ingestion of an additional 1 pCi/day (0.0015 mg/day) of soluble natural uranium would lead to a fractional increase in the incidence rate of osteogenic sarcoma (bone cancer) of 0.0019. This means that over a period of 70 years (the nominal lifetime length), if everyone were exposed at that level, the number of bone cancer cases in a U.S. population of 250 million would increase from 183,750 to about 184,100. Currently, there are no unequivocal studies that show that intake of natural or depleted uranium can induce radiation effects in humans or animals. The available information on humans and animals suggests that intake of uranium at the low concentrations usually ingested by humans or at levels found at or near hazardous waste sites is not likely to cause cancer. The BEIR IV committee, therefore, concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect."

Exposure to enriched uranium, used as uranium fuel in nuclear energy production, may present a radiological health hazard. Although uranium-associated cancers have not been identified in humans, even following exposure to highly enriched uranium, higher doses associated with highly enriched, high specific activity uranium may be able to produce bone sarcomas in humans. Evidence from animal studies suggests that high radiation doses associated with large intakes of ^{234}U and ^{235}U-enriched uranium compounds can be hazardous. Adverse effects reported from such exposures include damage to the interstitium of the lungs (fibrosis) and cardiovascular abnormalities (friable vessels). However, access to ^{235}U-enriched or other high specific-activity uranium is strictly regulated by the NRC and the U.S. Department of Energy (DOE). Therefore, the potential for human exposure to this level of radioactivity is limited to rare accidental releases in the workplace.

The potential for adverse noncancerous radiological health effects from uranium is dependent on several factors, including physicochemical form and solubility, route of entry, distribution in the various body organs, the biological retention time in the various tissues, and the energy and intensity of the radiation. The potential for such effects is generally thought to be independent of the known chemical toxicity of uranium. While the chemical properties affect the distribution and biological half-life of a radionuclide, the damage from radiation is independent of the source of that radiation. In this profile, there is little, or equivocal, specific information regarding the influence of radiation from uranium on certain biological effect end points in humans, such as reproductive, developmental, or carcinogenic effects. There is evidence, however, from the large body of literature concerning radioactive substances that alpha radiation can affect these processes in humans (see Appendix D for additional information on the biological effects of radiation). However, because the specific activities of natural and depleted uranium are low, no radiological health hazard is expected from exposure to natural and depleted uranium. Since the radiological component of natural uranium has essentially been discounted as a significant source of health effects, this leaves only the chemical effects of uranium to contend with. The chemical (non-radiological) properties of natural uranium and depleted uranium are identical; therefore, the health effects exerted by each are expected to be the same. The results of the available studies in humans and animals are consistent with this conclusion. The potential health impacts of depleted uranium are specifically addressed in a recent Department of Energy publication (DOE 1999).

Uranium is a heavy metal that forms compounds and complexes of different varieties and solubilities. The chemical action of all isotopes and isotopic mixtures of uranium is identical, regardless of the specific activity (i.e., enrichment), because chemical action depends only on chemical properties. Thus, the chemical toxicity of a given amount or weight of natural, depleted, and enriched uranium is identical.

The toxicity of uranium varies according to its chemical form and route of exposure. On the basis of the toxicity of different uranium compounds in animals, it was concluded that the relatively more water-soluble compounds (uranyl nitrate hexahydrate, uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranium pentachloride) were the most potent renal toxicants. The less water-soluble compounds (sodium diuranate, ammonium diuranate) were of moderate-to-low renal toxicity, and the insoluble compounds (uranium tetrafluoride, uranium trioxide, uranium dioxide, uranium peroxide, triuranium octaoxide) had little potential to cause renal toxicity but could cause pulmonary toxicity when exposure was by inhalation. *The terms soluble, moderately soluble, and insoluble are often used in this profile without relisting the specific compounds.* Generally, hexavalent uranium, which tends to form soluble compounds, is more likely to be a systemic toxicant than tetravalent uranium, which forms insoluble compounds. Ingested uranium is less toxic than inhaled uranium, which may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only <0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract (Leggett 1989). The available data on a variety of uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity (chemical toxicity) in humans. This low order results from the high exposures to which animals in these studies were exposed without adverse effects in many cases. The ICRP (1995) recommends a gastrointestinal absorption fraction of 0.02 (i.e. 2%) for uranium ingested in relatively stable form.

The hazard from inhaled uranium aerosols, or any noxious agent, is determined by the likelihood that the agent will reach the site of its toxic action. Two main factors that influence the degree of hazard from toxic airborne particles are the site of deposition in the respiratory tract of the particles and the fate of the particles within the lungs. The deposition site within the lungs depends mainly on the particle size of the inhaled aerosol, while the subsequent fate of the particle depends mainly on the physical and chemical properties of the inhaled particles and the physiological status of the lungs.

Human and animal studies have shown that long-term retention in the lungs of large quantities of inhaled insoluble uranium particles (e.g., carnotite dust [4% uranium as uranium dioxide and triuranium octaoxide, 80–90% quartz, and <10% feldspar]) can lead to serious respiratory effects. However, animals exposed to high doses of purified uranium (as uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetraoxide, uranium fluoride, or uranium acetate) through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures failed to develop these respiratory ailments. The lack of significant pulmonary injury in animal studies with insoluble compounds indicates that other factors, such as diverse inorganic particle abrasion or chemical reactions, may contribute to these effects.

Highly soluble forms of uranium clear the lungs quickly and are less likely to react with or affect the normal physiology of lung parenchymal tissue. In animal studies and in studies following intense accidental human exposure to uranium hexafluoride, hydrogen fluoride gas (a hydrolysis product of uranium hexafluoride) was suggested to have caused the observed pulmonary injury. Longer-term inhalation exposures to tolerable levels of uranium hexafluoride in animals, however, have caused renal toxicity.

Because natural uranium produces very little radioactivity per mass of uranium, the renal and respiratory effects from exposure of humans and animals to uranium are usually attributed to the chemical properties of uranium. However, in exposures to more radioactive uranium isotopes (e.g., ^{232}U and ^{233}U, and naturally occurring ^{234}U and ^{235}U), it has been suggested that the chemical and radiological toxicity may be additive or may potentiate in some instances. In these instances, this dual mode of uranium toxicity may not be distinguishable by end point because of the overlap of etiology and manifested effects. The mechanism of this interaction is as yet unclear.

In animals, kidney damage is the principal toxic effect of uranium, especially to its soluble compounds. The kidneys have been identified as the most sensitive target of uranium toxicosis, consistent with the metallotoxic action of a heavy metal. The toxic action is mediated by accumulation of uranium in the renal tubular epithelium which induces cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubule in humans and animals. Heavy metal ions, such as uranyl ions, are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis. These renal effects observed in animals can also occur in humans if the uranium dose is high enough. However, these effects have only been seen in certain acute poisoning incidents in humans. Epidemiological studies of uranium miners and mill workers have not demonstrated unusual rates of kidney disease. A recent comparison of kidney tissue obtained at autopsy from 7 uranium workers and 6 referents with no known exposure to uranium showed that the groups were indistinguishable by pathologists experienced in uranium-induced renal pathology. One study in humans found a dose-response nephrotoxicity, indicated by the presence of β_2-microglobulinuria and aminoaciduria from decreased tubular reabsorption, in 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the then current occupational standard of 1.0×10^{-10} µCi/mL (3.7 Bq/m^3) (0.15 mg/m^3) by up to 8-fold. However, the negative findings regarding renal injury among current uranium miners and mill workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure.

A histological kidney study of chronically exposed workers found no pathological differences at the low kidney concentrations (~0.3 µg/g) when compared to unexposed workers (Russell et al. 1996). In animal studies, observations in acute- and intermediate-duration exposures to uranium compounds conclusively show that high doses of uranium are nephrotoxic. Histopathological examination of the kidneys of these animals following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, and decreased glomerular filtration rates. The damage in animals is histologically manifested as glomerular and tubular wall pathology. A mechanism involving bicarbonate uptake in the kidneys and subsequent precipitation of uranium in the tubule was proposed for uranium-induced renal toxicity. An alternative mechanism involving the inhibition of both sodium transport-dependent and transport-independent adenosine triphosphate (ATP) utilization and of mitochondrial oxidative phosphorylation in the renal proximal tubule has also been proposed.

Respiratory diseases have been associated with human exposure to the atmosphere in uranium mines. Respiratory diseases in uranium miners (fatal in some cases) have been linked to exposure to silica dust, oxide dusts, diesel fumes, and radon and its daughters, in conjunction with cigarette smoking. In several of these studies, the investigators concluded that, although uranium mining clearly elevates the risk for respiratory disease, uranium contributes minimally, if at all, to this risk. The mine air also contained radon and its daughters, and cigarette smoke, which are proven carcinogens. As in human studies, several animal studies in which uranium-containing dusts, such as carnotite uranium dust, were used reported the occurrence of respiratory diseases.

Epidemiologic studies among workers who had been exposed to uranium aerosols in strip and underground mines, mills, and processing facilities found more than the expected number of lung cancers only among underground miners and especially among miners who were cigarette smokers. No significant difference in the incidence rate of lung cancer was found between other workers who had been occupationally exposed to uranium and control populations. In addition to uranium dust, the mine air contained many other noxious aerosols (including silica, oxides of nickel, cobalt, and vanadium), radon and its daughters, diesel fumes, and cigarette smoke. Excess cancers were found among those underground miners whose radon daughter exposure exceeded 120 working level months (WLM). The rate of cancer incidence increased with increasing exposure to radon daughters.

No significant difference in cancer (of the lungs) was found between workers who are occupationally exposed to uranium and control populations. Other detailed studies conducted between 1950 and 1967 on the association between uranium mining and an increased incidence of cancer found lung cancer in the

miners over six times the rate expected. However, some of the miners were exposed to other potentially cancer-causing substances such as radon and its progeny, tobacco smoke, diesel smoke, and solvents (carbon tetrachloride and trichloroethylene). These studies and a review of 11 uranium miner studies attributed the increased incidence of lung cancer to radon and its progeny and not to uranium.

The evidence for the cancer-inducing potential of uranium in animals is also inconclusive. Animals exposed to very high doses of uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetroxide, uranyl fluoride, uranium tetrafluoride, or uranium acetate, through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures, failed to develop these respiratory cancers. The lack of significant pulmonary injury in oral animal studies indicates that other factors such as diverse inorganic dust or radon daughters may contribute to these effects. Because uranium is a predominantly alpha-emitting radionuclide, current theories on cellular necrosis by high linear energy transfer (LET) alpha radiation also imply a contributory role to the cellular degenerative pulmonary changes. In studies in which human subjects and animals were exposed to uranium hexafluoride, hydrogen fluoride was probably responsible for, or aggravated, the observed respiratory effects. Uranium hexafluoride is hydrolyzable to uranyl fluoride and hydrogen fluoride, and death occurred shortly after intake with signs and symptoms of acute acid-induced cellular damage.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites or potential hazardous wastes sites containing uranium, the information in this section is organized first by route of exposure—inhalation, oral, and dermal; by health effects— death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and cancer effects; and then by chemical and radiation effects. Regarding the last aggregation of the data, the chemical and radiological identities of uranium are discussed, for the purpose of presentation only, as separate concerns. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration 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 doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death,

or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. For noncancer radiological effects, the actual dose or exposure at which the effects occurred or were observed is designated the radiation effect level.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste 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 (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with health effects by route of exposure to uranium are indicated in Tables 2-1 and 2-2 and Figures 2-1 and 2-2. Data permitting, the cancer effects of uranium are discussed separately with respect to chemical and radiation etiology.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for uranium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive the MRLs (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an

example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

The toxicity of uranium compounds to the lungs and distal organs varies when exposed by the inhalation route. In general, the more soluble compounds (uranyl fluoride,[1] uranium tetrachloride, uranyl nitrate hexahydrate) are less toxic to the lungs but more toxic systemically by the inhalation route due to easier absorption from the lungs into the blood and transportation to distal organs (Tannenbaum and Silverstone 1951). A study summary of the data for inhalation toxicity (lethality) studies in mice exposed to equivalent uranium concentrations of uranium tetrafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate, or triuranium octaoxide concluded that the order of decreasing systemic toxicity for these compounds may be as follows: very toxic, uranyl fluoride; toxic, uranyl nitrate hexahydrate; and nontoxic (at the levels tested in companion studies), uranium tetrachloride, uranium tetrafluoride, and triuranium octaoxide (Stokinger et al. 1953; Tannenbaum and Silverstone 1951). Although uranium tetrachloride is highly soluble in water, it is easily hydrolyzed and oxidized into less soluble uranyl chloride and insoluble

[1] Uranium hexafluoride is hydrolyzed to uranyl fluoride and hydrogen fluoride. Hydrogen fluoride is highly toxic in acute exposures and causes pulmonary edema, which may be immediately life-threatening.

uranium dioxide. For this reason, inhaled uranium tetrachloride tends not to behave as if it is a highly soluble uranium compound. Conversely, the more common insoluble salts and oxides (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) are generally more toxic to the lungs through inhalation exposure because of the longer retention time in the lung tissue but they are less toxic to distal organs.

On the basis of the available data, the rabbit appears to be unusually susceptible to the lethal effects of uranium's metallotoxicity. The order of animal species susceptibility to acute uranium toxicity has been suggested as follows: rabbit > rat > guinea pig > pig > mouse (Orcutt 1949).

2.2.1.1 Death

The lethal effects of inhalation exposure to uranium have been investigated in humans in epidemiological studies and in animal studies under controlled conditions. Epidemiological studies indicate that routine exposure of humans (in the workplace and the environment at large) to airborne uranium is not associated with increased mortality. Brief accidental exposures to very high concentrations of uranium hexafluoride have caused fatalities in humans. Laboratory studies in animals indicate that inhalation exposure to certain uranium compounds can be fatal. These deaths are believed to result from renal failure caused by absorbed uranium. The low specific activity of uranium precludes the possibility of absorbing enough uranium to deliver a lethal dose of radiation.

No definitive evidence has been found in epidemiologic studies that links human deaths to uranium exposure. Among uranium miners, death rates from diseases of the cardiovascular system and the urogenital system were decreased compared to other populations. Uranium miners have higher-than-expected rates of death from lung cancer; however, this finding is attributed to the radiological effects of radon and its decay products, which are progeny of uranium and, therefore, present in uranium mines. In addition, the role of tobacco smoking in these deaths was not evaluated (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984, 1986). Epidemiologic studies of workers at uranium mill and metal processing plants (where there is little or no exposure to radon in excess of normal environmental levels) showed no increase in overall deaths attributable to exposure to uranium (Archer et al. 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Hadjimichael et al. 1983; Polednak and Frome 1981; Scott et al. 1972; Waxweiler et al. 1983).

Deaths occurred after accidental releases of uranium hexafluoride at uranium-processing facilities in 1944 and 1986, but these deaths were not attributed to the uranium component of this compound (Kathren and

Moore 1986; Moore and Kathren 1985; USNRC 1986). These releases resulted in the generation of concentrated aerosols of highly toxic hydrofluoric acid and uranyl fluoride[2]. In the 1944 incident exposure time was estimated to be only 17 seconds, deaths occurred in 2 of 20 workers within an hour and were attributed to severe chemical burns of the lungs. In the 1986 incident, 1 of 23 workers died from massive pulmonary edema, indicating that inhalation of hydrofluoric acid was responsible for death. Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively).

Mortality can be induced in animals exposed to sufficiently high concentrations of pure uranium compounds. The acute-duration LC_{50} (lethal concentration, 50% death) for uranium hexafluoride has been calculated for Long-Evans rats and Hartley guinea pigs (Leach et al. 1984). The animals were exposed to uranium hexafluoride in a nose-only exposure apparatus for periods of up to 10 minutes and then observed for 14 days. Total mortality in rats was 34% (157/460): 25% of the deaths occurred during exposure or within 48 hours, 59% between days 3 and 7, and 17% between days 7 and 14. Guinea pigs were more sensitive than rats; total mortality was 46% (36/78), and 64% of deaths occurred within 48 hours. In guinea pigs, the LC_{50} was estimated as 35,011 mg U/m^3 for a 2-minute exposure limit. For a 5-minute inhalation exposure, the LC_{50} in Long-Evans rats was estimated as 26,098 mg U/m^3; the LC_{50} for a 10-minute inhalation was estimated as 8,114 mg U/m^3. The animals that died showed some damage to the respiratory tract, probably due to hydrofluoric acid, but this damage was not judged to be the cause of death, at least in the animals that died more than 2 days postexposure. Urinalysis and histopathological examination indicated that renal injury was the primary cause of death (Leach et al. 1984). In other acute lethality studies, rats, mice, and guinea pigs suffered 10, 20, and 13% mortality, respectively, following a 10-minute inhalation of uranium hexafluoride corresponding to 637 mg U/m^3 (Spiegl 1949).

In intermediate-duration studies, rabbits and cats were generally the most sensitive species to uranium lethality. Deaths in these studies generally occurred beginning 2 weeks after exposure started and continued to the end of the experiment. Exposure to 2 mg U/m^3 (as uranium hexafluoride) 6 hours a day for 30 days caused 5, 20, and 80% mortality in guinea pigs, dogs, and rabbits, respectively (Spiegl 1949). An exposure to 9.5 mg U/m^3 (as uranyl nitrate hexahydrate) for 8 hours per day, 5 days per week for 30 days caused 10% mortality in rats and guinea pigs, and 75% mortality in dogs. Exposure to 2 mg U/m^3 killed all four cats tested (Roberts 1949). Exposure to 9.2 mg U/m^3 (as uranyl fluoride) 6 hours a day, 5.5 days a week for 5 weeks caused 0%, 100%, 83%, and 55% mortality in rats, mice, rabbits and guinea pigs, and deaths in two dogs and two cats tested at this concentration (Rothstein

[2] Uranium hexafluoride rapidly dissociates into hydrofluoric acid and uranyl fluoride on contact with moisture in the air.

1949a). The lowest exposure causing death with uranyl fluoride was 0.15 mg U/m^3 in mice and rabbits and 2.2 mg U/m^3 in guinea pigs. Exposure to 15.4 mg U/m^3 (as uranium peroxide) 5 hours a day, 5 days a week for 23 days caused 10, 63, 40, 80, and 100% mortality in rats, mice, guinea pigs, rabbits, and cats, respectively, while 9.2 mg U/m^3 killed all the dogs tested (Dygert 1949d). Inhalation of air containing 15 mg U/m^3 (as sodium diuranate) for 6 hours a day, 5.5 days a week for 5 weeks caused 13 and 28% mortality in guinea pigs and rabbits, respectively (Rothstein 1949d).

Insoluble uranium compounds were also lethal to animals by the inhalation route, but at higher concentrations than with soluble compounds. Exposure to 15.8 mg U/m^3 (as uranium trioxide) 6 hours a day, 5.5 days a week for 4 weeks caused 10, 9, 17, and 67% mortality in rats, guinea pigs, dogs, and rabbits, respectively (Rothstein 1949c). Inhalation of air containing 19.4 mg U/m^3 (as uranium dioxide) for 6 hours a day, 5.5 days a week for 5 weeks, caused 60% mortality in rabbits but no mortality in rats, mice, guinea pigs, or dogs (Rothstein 1949b). Inhalation of air containing 18 mg U/m^3 (as uranium tetrafluoride) for 5 hours a day for 30 days caused 15, 32, 33, and 100% mortality in guinea pigs, rats, rabbits, and cats, respectively, and death in a single dog tested at this concentration. Inhalation at 4 mg U/m^3 caused no deaths in a group of 18 dogs, and one death in a group of 30 rats (Dygert 1949a). A mortality of 4% was observed among rabbits given 3 mg U/m^3 (Stokinger et al. 1953). Exposure to 6.8 mg U/m^3 (as ammonium diuranate) 6 hours a day for 30 days caused 20 and 100% mortality in guinea pigs and rabbits, respectively (Dygert 1949b).

In chronic-duration experiments, inhalation of 2 mg U/m^3 as uranyl nitrate hexahydrate for 6 hours a day, 5.5 days a week for 92–100 weeks resulted in 1% mortality in rats (Stokinger et al. 1953). This is not an unusual mortality rate for rats, so it is unlikely that these deaths can be attributed to uranium exposure. Dogs exposed to uranyl nitrate hexahydrate for 2 years suffered 4% mortality (Stokinger et al. 1953). One dog died at 0.25 mg U/m^3, and another at 2 mg U/m^3 out of 25 exposed dogs. Death may or may not have been attributable to uranium, according to the study investigator.

In several other inhalation-exposure animal studies, no deaths were observed when either soluble or insoluble uranium compounds were administered. In one of these animal studies, no mortality was observed in monkeys exposed by inhalation to uranium dioxide dust at a concentration of 5 mg U/m^3 for 5 years. The death of Beagle dogs similarly exposed could not be attributed to uranium by the investigators (Leach et al. 1970).

The percent mortality values for each species and other LOAEL values for mortality from exposure to uranium by the inhalation route are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

No human studies were located regarding the cardiovascular, musculoskeletal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects of elemental uranium following acute-duration inhalation exposure. Nor were any human studies located regarding the respiratory, hematological, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects of uranium following intermediate-duration inhalation exposure. No studies were found regarding the cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects in humans following chronic-duration inhalation exposure. The existing human data on the respiratory and hepatic effects of uranium are limited to acute- and chronic-duration inhalation exposures, hematological effects are limited to chronic-duration inhalation exposure, and gastrointestinal and renal effects are limited to acute-duration inhalation exposure.

No animal studies were located regarding the endocrine, metabolic, dermal, or ocular effects of uranium in animals following acute-duration inhalation exposures to uranium. Nor were any studies located regarding the metabolic, dermal, ocular, or other systemic effects in animals following intermediate-duration inhalation exposure to uranium. There are animal data for acute-, intermediate-, and chronic-duration inhalation exposures to uranium for respiratory, hematological, cardiovascular, gastrointestinal, renal, or body weight effects. However, animal data on hepatic effects are limited to acute- and chronic-duration inhalation exposures to uranium.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for systemic effects from chemical exposure to uranium by the inhalation route are presented in Table 2-1 and plotted in Figure 2-1. The radiation effect level values in each species and duration category for systemic effects from radiation exposure to uranium by the inhalation route are presented in Table 2-2 and plotted in Figure 2-2.

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Long-Evans)	10 min				630 M (1/10 died)	Leach et al. 1984 *** UF6
2	Rat (Long-Evans)	5 min				6470 M (1/10 died on day 7 postexposure)	Leach et al. 1984 *** UF6
3	Rat (NS)	1 d 10 min				637 (10% mortality 30 days post-exposure)	Spiegl 1949 UF6
4	Mouse (NS)	1 d 10 min				637 (20% mortality 30 days post-exposure)	Spiegl 1949 UF6
5	Gn Pig (Hartley)	2 min				23040 M (2/6 died 48 hrs postexposure)	Leach et al. 1984 *** UF6
6	Gn Pig (NS)	1 d 10 min				637 (13% mortality 30 days post-exposure)	Spiegl 1949 UF6
Systemic							
7	Rat (Long-Evans)	10 min	Renal		426 M (proteinuria, glucosuria, and polyuria)		Leach et al. 1984 *** UF6
8	Rat (Long-Evans)	2 min	Renal	920 M	1430 M (proteinuria)		Leach et al. 1984 *** UF6
9	Rat (Long-Evans)	5 min	Resp		9131	54503 M (severe nasal congestion, hemorrhage)	Leach et al. 1984 *** UF6
			Renal		392 M (glucosuria)		

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
10	Rat (NS)	1 d 10 min	Resp			637 (gasping in 100% of rats; severe irritation of nasal passages)	Spiegl 1949 UF6
			Renal			637 (severe degeneration of renal cortical tubules 5-8 days post-exposure)	
			Ocular		637 (conjunctivitis)		
11	Mouse (NS)	1 d 10 min	Resp			637 (gasping in 100% of mice; severe irritation of nasal passages)	Spiegl 1949 UF6
			Ocular		637 (conjunctivitis)		
12	Gn Pig (Hartley)	2 min	Renal		23040 M (glucosuria and polyuria)		Leach et al. 1984 *** UF6
13	Dog [Beagle]	once 0.5-1 hr	Resp	270			Morrow et al. 1982 *** UO2F2
			Renal			250 (extensive degeneration in kidney cortex and tubules)	
	Immunological/Lymphoreticular						
14	Rat (Fischer-344)	once			44 M (increased macrophage activity)		Morris et al. 1989 *** UO2
15	Rat (Fischer-344)	once			132 M (increased macrophage activity)		Morris et al. 1992 *** UO2
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (NS)	30 d 6 hr/d				4 (3% mortality)	Dygert 1949a UF4

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
17	Rat (NS)	23 d 5 d/wk 5 hr/d				15.4 (10% mortality)	Dygert 1949d UO4
18	Rat (NS)	30 d Cont.				9.5 (10% mortality)	Roberts 1949 UO2(NO3)2*6H2O
19	Rat (NS)	4 wk 6 d/wk 6 hr/d				15.8 (10% mortality)	Rothstein 1949c UO3
20	Mouse (NS)	23 d 5 d/wk 5 hr/d				15.4 (63% mortality)	Dygert 1949d UO4
21	Gn Pig (NS)	30 6 hr/d				18 (15% mortality)	Dygert 1949a UF4
22	Gn Pig (NS)	30 d 6 hr/d				6.8 (20% mortality)	Dygert 1949b (NH4)2U2O7
23	Gn Pig (NS)	23 d 5 d/wk 5 hr/d				15.4 (40% mortality)	Dygert 1949d UO4
24	Gn Pig (NS)	30 d Cont.				9.5 (10% mortality)	Roberts 1949 UO2(NO3)2*6H2O
25	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d				2.2 (3% mortality)	Rothstein 1949a UO2F2
26	Gn Pig (NS)	4 wk 6 d/wk 6 hr/d				15.8 (9% mortality)	Rothstein 1949c UO3

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
27	Gn Pig (NS)	5 wk 5.5 d/wk 6 hr/d				15 (13% mortality)	Rothstein 1949d Na2U2O7
28	Gn Pig (NS)	30 d 6 hr/d				2 (5% mortality)	Spiegl 1949 UF6
29	Dog (NS)	30 d 6 hr/d				18 (lethal dose)	Dygert 1949a UF4
30	Dog (NS)	30 d Cont.				9.5 (75% mortality)	Roberts 1949 UO2(NO3)2*6H2O
31	Dog (NS)	5 wk 6 d/wk 6 hr/d				9.2 (100% mortality)	Rothstein 1949a UO2F2
32	Dog (NS)	4 wk 6 d/wk 6 hr/d				15.8 (17% mortality)	Rothstein 1949c UO3
33	Dog (NS)	30 d 6 hr/d				2 (20% mortality)	Spiegl 1949 UF6
34	Rabbit (NS)	30 d 6 hr/d				18 (33% mortality)	Dygert 1949a UF4
35	Rabbit (NS)	30 d 6 hr/d				6.8 (100% mortality)	Dygert 1949b (NH4)2U2O7
36	Rabbit (NS)	23 d 5 hr/d 5 d/wk				15.4 (80% mortality)	Dygert 1949d UO4
37	Rabbit (NS)	5 wk 6 d/wk				19.4 (60% mortality)	Rothstein 1949b UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
38	Rabbit (NS)	4 wk 6 d/wk 6 hr/d				15.8 (67% mortality)	Rothstein 1949c UO3
39	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d				15 (28% mortality)	Rothstein 1949d Na2U2O7
40	Rabbit (NS)	30 d 6 hr/d				2 (80% mortality)	Spiegl 1949 UF6
41	Rabbit	34 wk 5.5 d/wk 6 hr/d				3 (4% mortality)	Stokinger et al. 1953 UF4
42	Cat (NS)	30 d 6 hr/d				18 (100% mortality)	Dygert 1949a UF4
43	Cat (NS)	23 d 5 d/wk 5 hr/d				15.4 (100% mortality)	Dygert 1949d UO4
44	Cat (NS)	30 d Cont.				2 (100% mortality)	Roberts 1949 UO2(NO3)2*6H2O
	Systemic						
45	Rat (NS)	30 d 6 hr/d	Gastro		0.4 (ulceration of cecum)		Dygert 1949a UF4
			Hemato	18			
			Hepatic		0.4 (focal necrosis of liver)		
			Renal	4	18 (slight azotemia)		
			Bd Wt	4		18 (26% decrease body weight)	

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
46	Rat (NS)	30 d 6 hr/d	Resp		6.8 (intersitial bronchopneumonia in 25% of animals; nasal irritation)		Dygert 1949b (NH4)2U2O7
			Hemato		6.8 (decreased RBC, hemoglobin)		
			Renal		6.8 (minimal necrosis of tubular epithelium followed by regeneration)		
			Bd Wt	6.8			
47	Rat (NS)	26 d 4-6 hr/d	Resp	4.8			Dygert 1949c U3O8
			Cardio	4.8			
			Hemato	4.8			
			Hepatic	4.8			
			Renal		4.8 (renal degeneration indicated by moderate regeneration)		
			Bd Wt	4.8			
48	Rat (NS)	30 d Cont.	Hemato	2.1	9.5 (decreased RBC, hemoglobin)		Roberts 1949 UO2(NO3)2*6H2O
			Renal		0.13 (slight renal tubular degeneration in 33% after 28 days exposure)		
			Bd Wt	2.1	9.5 (5.6-12.6% decreased body weight)		
49	Rat (NS)	5 wk 6 d/wk 6 hr/d	Hemato	9.2			Rothstein 1949a UO2F2
			Renal	0.5	2.2 (minimal renal tubular degeneration)		
			Bd Wt	2.2	9.2 (unspecified moderate weight loss)		

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
50	Rat (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight degenerative changes in the lungs)			Rothstein 1949c UO3
			Hemato		16	(increased percentage of myeloblasts and lymphoid cells of bone marrow)			
			Hepatic	16					
			Renal	16					
			Bd Wt	16					
51	Rat (NS)	5 wk 5.5 d/wk 6 hr/d	Hemato	15					Rothstein 1949d Na2U2O7
			Renal		15	(moderate renal degeneration and necrosis)			
52	Rat (NS)	30 d 6 hr/d	Resp	2			13	(pulmonary edema, hemorrhage, emphysema; inflammation of bronchi, alveoli and alveolar interstices)	Spiegl 1949 UF6
			Hemato	13					
			Ocular	2	13	(eye irritation)			
			Bd Wt	13					
53	Rat (NS)	30 d 6 hr/d	Hemato	0.2					Spiegl 1949 UF6
			Renal	0.2					
			Bd Wt	0.2					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
54	Mouse (NS)	30 d 4.4-6 hr/d	Resp	2.9					Pozzani 1949 Carnotite U ore
			Hepatic	2.9					
			Renal		2.9	(slight renal tubular degeneration)			
			Bd Wt	2.9					
55	Mouse (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b UO2
			Hemato	19.4					
			Renal	19.4					
			Bd Wt	19.4					
56	Mouse (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema; inflammation of bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration followed by regeneration, and necrosis, and the presence of casts in the tubules)	
			Ocular	2	13	(eye irritation)			
			Bd Wt	2	13	(unspecified weight loss)			
57	Gn Pig (NS)	30 d 6 hr/d	Hemato	18					Dygert 1949a UF4
			Renal	4			18	(moderate to severe necrosis of corticomedullary tubular epithelium)	

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
58	Gn Pig (NS)	30 d 4.4-6 hr/d	Resp	2.9					Pozzani 1949 Carnotite U ore
			Hepatic	2.9					
			Renal	0.8	2.9	(micoscopic focal lesions in renal tubular epithelium in 1/5 guinea pigs)			
			Bd Wt	2.9	22	(14% decreased body weight in animals that died)			
59	Gn Pig (NS)	30 d Cont.	Bd Wt	2.1			9.5	(2.9-27.9% decreased body weight)	Roberts 1949 UO2(NO3)2*6H2O
60	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d	Renal	2.2			9.2	(severe degeneration of renal tubular epithelium)	Rothstein 1949a UO2F2
			Bd Wt		2.2	(unspecified moderate weight loss)			
61	Gn Pig (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema, acute inflammation was seen in the bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration, necrosis, regeneration; casts in the tubules)	
			Bd Wt	2	13	(13% decreased body weight)			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
62	Gn Pig (NS)	30 d 6 hr/d	Resp	2			13	(lung edema, hemorrhage, and emphysema, acute inflammation was seen in the bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 UF6
			Renal	2			13	(severe renal-tubular degeneration, necrosis, regeneration; casts in the tubules)	
			Bd Wt	2	13	(13% decreased body weight)			
63	Gn pig	30 wk 5.5 d/wk 6 hr/d	Renal		0.2	(minimal microscopic lesions in tubular epithelium)			Stokinger et al. 1953 UCl4
64	Gn pig (NS)	28 wk 5.5 d/wk 6 hr/d	Renal	10					Stokinger et al. 1953 UO2
			Bd Wt	10					
65	Gn pig (NS)	26 wk 5.5 d/wk 6 hr/d	Hemato	2 M					Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal	2 M					
			Bd Wt	2 M					
66	Gn pig	34 wk 5.5 d/wk 6 hr/d	Hemato	3					Stokinger et al. 1953 UF4
			Renal		3	(minimal microscopic lesions in renal tubule)			
			Bd Wt	3					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
67	Gn pig	36 wk 5.5d/wk 6 hr/d	Renal	0.2					Stokinger et al. 1953 UF6
			Bd Wt	0.2					
68	Dog (NS)	30 d 6 hr/d	Resp	4	18	(rhinitis)			Dygert 1949a UF4
			Gastro	4			18	(vomited blood)	
			Hemato	18					
			Renal	0.5	3	(very slight degenerative changes in tubular epithelium)			
			Ocular	4	18	(conjunctivitis)			
			Bd Wt	4			18	(26% decreased body weight)	
69	Dog (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4					Dygert 1949d UO4
			Bd Wt	15.4					
70	Dog (NS)	30 d 4.4-6 hr/d	Resp	0.8	2.9	(hemorrhagic lungs)			Pozzani 1949 Carnotite U ore
			Hemato	2.9					
			Hepatic	2.9					
			Renal		0.8	(mild renal tubular degeneration)			
			Bd Wt	2.9					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
71	Dog (NS)	30 d Cont.	Resp	2.1	9.5	(rales; slight degeneration in lung epithelium)			Roberts 1949 UO2(NO3)2*6H2O
			Gastro	2.1	9.5	(vomiting, anorexia)			
			Hemato		0.13	(slightly decreased fibrinogen)			
			Renal		0.13	(proteinuria, transient increase in bromosulfalein retention)			
			Bd Wt	2.1			9.5	(approximately 25% decreased body weight in 3/4 that died)	
			Other	2.1					
72	Dog (NS)	5 wk 6 d/wk 6 hr/d	Resp	2.2	9.2	(rhinitis)			Rothstein 1949a UO2F2
			Gastro	2.2			9.2	(vomited blood)	
			Hemato	9.2					
			Renal		0.15[b]	(very slight renal degeneration in approximately 50% of dogs)			
			Bd Wt	2.2			9.2	(unspecified severe weight loss)	
73	Dog (NS)	5 wk 6 d/wk	Resp	9.2					Rothstein 1949b UO2
			Hemato	9.2					
			Renal	1.1[c]	8.2	(slight renal tubular degeneration in 2/6)			
			Bd Wt	9.2					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
74	Dog (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight pulmonary degenerative changes)			Rothstein 1949c UO3
			Hemato	16					
			Hepatic	16					
			Renal		16	(mild degeneration in glomerulus; diuresis)			
			Bd Wt	16					
75	Rabbit (NS)	30 d 6 hr/d	Hemato	18					Dygert 1949a UF4
			Renal		0.4	(increased urinary catalase and phosphatase)			
			Bd Wt	3			18	(24% decreased body weight)	
76	Rabbit (NS)	30 d 6 hr/d	Resp				6.8	(pulmonary edema, hemorrhage, and necrosis)	Dygert 1949b (NH4)2U2O7
			Hemato		6.8	(increased neutrophils, decreased lymphocytes)			
			Renal				6.8	(severe necrosis of the tubular epithelium)	
77	Rabbit (NS)	23 d 5 d/wk 5 hr/d	Resp				15.4	(edematous alveoli, alveolar hemorrhage, hyperemia, and atelectasis)	Dygert 1949d UO4
			Hemato	15.4					
			Hepatic	15.4					
			Renal		15.4	(moderate corticomedullary tubule necrosis with regeneration of tubular cells; azotemia)			
			Bd Wt	15.4					

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
78	Rabbit (NS)	30 d 4.4-6 hr/d	Resp	2.9			22	(moderate to severe pulmonary lesions)	Pozzani 1949 Carnotite U ore
			Hemato	22					
			Hepatic	22					
			Renal	0.8	2.9	(moderate kidney tubular degeneration)			
			Bd Wt	2.9	22	(11% decreased body weight in dying rabbits)			
79	Rabbit (NS)	30 d Cont.	Resp	0.2					Roberts 1949 UO2(NO3)2*6H2O
			Hemato		0.13	(increased plasma prothrombin and fibrinogen)			
			Renal		0.13	(increased urinary catalase)			
			Bd Wt	0.13	0.2	(unspecified decrease in body weight)			
80	Rabbit (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b UO2
			Hemato	19.4					
			Renal	9.2			19	(severe tubular necrosis in dying animals)	
			Bd Wt	8.2	9.2	(unspecified decreased body weight)			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
81	Rabbit (NS)	4 wk 6 d/wk 6 hr/d	Resp				16	(hemorrhage and consolidation in lungs of animals that died)	Rothstein 1949c UO3
			Hemato	16					
			Hepatic		16	(moderate fatty livers in 5/8 animals that died)			
			Renal		16	(mild to severe necrosis of the tubular epithelium with degeneration and regeneration; increased NPN)			
			Bd Wt	16					
82	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d	Hepatic		15	(slight decrease in lactate)			Rothstein 1949d Na2U2O7
			Renal		15	(progressive degeneration and necrosis followed by regeneration of tubular epithelium; increased NPN)			
			Bd Wt	15					
83	Rabbit (NS)	30 d 6 hr/d	Hemato	13					Spiegl 1949 UF6
			Bd Wt	0.2	2	(12% decreased body weight)			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
84	Rabbit (NS)	26 wk 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2			
			Renal		0.25 (increased urinary catalase; minimal microscopic lesions in renal tubule)		
			Bd Wt	2			
85	Rabbit	34 wk 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UF4
			Renal		2 (minimal microscopic lesions in renal tubule)		
			Bd Wt	2			
86	Rabbit (NS)	30 wk 5.5 d/wk 6 hr/d	Hemato	1			Stokinger et al. 1953 UO2
			Renal		1 (minimal microscopic lesions in renal tubule)		
			Bd Wt	1			
87	Rabbit	36 wk 5.5 d/wk 6 hr/d	Hemato	0.25			Stokinger et al. 1953 UF6
			Renal		0.25 (minimal microscopic lesions in renal tubule)		
			Bd Wt	0.25			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
88	Cat (NS)	30 d 6 hr/d	Resp		18 (rhinitis)		Dygert 1949a UF4
			Gastro			18 (vomited blood)	
			Hemato	18			
			Renal			18 (moderate to severe typical renal injury in 2/3 dying cats; azotemia)	
			Ocular		18 (conjunctivitis)		
			Bd Wt		18 (18% decreased body weight)		
89	Cat (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4			Dygert 1949d UO4
			Renal			15.4 (azotemia)	
			Bd Wt	15.4			
90	Cat (NS)	5 wk 6 d/wk 6 hr/d	Resp	2.2	9.2 (rhinitis)		Rothstein 1949a UO2F2
			Gastro	2.2		9.2 (vomited blood prior to death)	
			Renal	2.2		9.2 (severe degeneration of renal tubular epithelium)	
91	Cat (NS)	4 wk 6 d/wk 6 hr/d	Hemato	16			Rothstein 1949c UO3
			Renal		16 (diuresis; proteinuria; increased NPN)		
			Bd Wt	16			
Immunological/Lymphoreticular							
92	Rat (NS)	30 d 6 hr/d			0.4 (edematous cecal lymph nodes; focal necrosis of spleen)		Dygert 1949a UF4

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3		LOAEL Serious mg U/m3		Reference Chemical Form
93	Rat (NS)	30 d 6 hr/d			6.8	(rise in neutrophils, decreased lymphocytes, moderate fall in the white blood count, rise in the eosinophils)			Dygert 1949b (NH4)2U2O7
94	Rat (NS)	30 d Cont.		2.1	9.5	(decreased absolute number of lymphocytes and neutrophils)			Roberts 1949 UO2(NO3)2*6H2O
	Neurological								
95	Dog (NS)	30 d 6 hr/d		4	18	(weakness and unsteady gait)			Dygert 1949a UF4
96	Dog (NS)	5 wk 6 d/wk 6 hr/d		2.2			9.2	(anorexia, severe muscle weakness, lassitude)	Rothstein 1949a UO2F2
97	Cat (NS)	30 d 6 hr/d			18	(weakness and unsteady gait)			Dygert 1949a UF4
98	Cat (NS)	5 wk 6 d/wk 6 hr/d		2.2			9.2	(anorexia, severe muscle weakness, lassitude)	Rothstein 1949a UO2F2
	CHRONIC EXPOSURE								
	Death								
99	Rat (NS)	92-100 wk 5.5 d/wk 6 hr/d					2	(1% mortality)	Stokinger et al. 1953 UO2(NO3)2*6H2O
100	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d					5	(4.5% mortality)	Leach et al. 1970 UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
101	Dog (NS)	2 yr 5.5 d/wk 6 hr/d				2 (9% mortality)	Stokinger et al. 1953 UO2(NO3)2*6H2O
	Systemic						
102	Monkey	5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary hyaline fibrosis)		Leach et al. 1970 UO2
			Hepatic	5.1			
			Renal	5.1			
			Bd Wt	5.1			
103	Monkey	1-5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary fibrosis)		Leach et al. 1973 UO2
			Hemato	5.1			
			Hepatic	5.1			
			Renal	5.1			
			Bd Wt	5.1			
104	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 UCl4
			Gastro	0.2			
			Hepatic	0.2			
			Renal		0.2 (minimal microscopic lesions in renal tubule)		
			Endocr	0.2			
			Bd Wt	0.2			
105	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Renal	0.15	0.25 (mild renal tubular atrophy)		Stokinger et al. 1953 UO2(NO3)2*6H2O
			Bd Wt	2			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
106	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 UF4
			Renal		0.5 (minimal microscopic lesions in renal tubule)		
			Bd Wt	3			
107	Rat	1 yr 5.5 d/wk 6 hr/d	Hemato	10			Stokinger et al. 1953 UO2
			Renal	1	10 (slight degenerative changes)		
			Bd Wt	10			
108	Rat (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal		2 (mild, acute tubular necrosis and regeneration)		
			Bd Wt	2			
109	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 UF6
			Cardio	0.2			
			Gastro	0.2			
			Hepatic	0.2			
			Renal	0.05	0.2 (mild renal tubular degeneration)		
			Endocr	0.2			
			Dermal	0.2			
			Bd Wt	0.2			

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
110	Dog (Beagle)	1-5 yrs 5 d/wk 5.4 hr/d	Resp	5.1			Leach et al. 1970 UO2
			Hemato	5.1			
			Renal	5.1			
			Bd Wt	5.1			
111	Dog (NS)	1-5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (minimal pulmonary fibrosis)		Leach et al. 1973 UO2
			Hemato	5.1			
			Renal	5.1			
			Bd Wt	5.1			
112	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	0.2			Stokinger et al. 1953 UCl4
			Hepatic	0.2			
			Renal	0.05[d]	0.2 (minimal microscopic lesions in renal tubule)		
			Bd Wt	0.2			
113	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2			
			Renal	0.15	0.25 (minimal microscopic lesions in renal tubule; transient increase in NPN)		
			Bd Wt	2			
114	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Renal	0.15	0.25 (minimal degeneration in renal tubule)		Stokinger et al. 1953 UO2(NO3)2*6H2O

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
115	Dog (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Renal		2 (mild tubular necrosis)		
116	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	0.05	0.2 (lengthened blood clotting time; decreased blood fibrinogen)		Stokinger et al. 1953 UF6
			Hepatic		0.2 (increased bromosulfalein retention)		
			Renal		0.05 (minimal microscopic lesions in renal tubule)		
			Bd Wt	0.2			
117	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 UO2(NO3)2*6H2O
			Hepatic	2			
			Renal	0.15	0.25 (minimal microscopic lesions in renal tubule; transient increase in NPN)		
			Bd Wt	2			
Immunological/Lymphoreticular							
118	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d			5.1 (minimal lymph node fibrosis)		Leach et al. 1970 UO2

Table 2-1. Levels of Significant Exposure to Uranium - Chemical Toxicity - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg U/m3	LOAEL Less serious mg U/m3	LOAEL Serious mg U/m3	Reference Chemical Form
Cancer							
119	Dog (NS)	1-5 yr 5 d/wk 5.4 hr/d				5.1 (CEL: lung cancer)	Leach et al. 1973 UO2

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an intermediate-duration inhalation MRL for soluble uranium compounds of 0.0004 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL for insoluble uranium compounds of 0.008 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variability).

[d] Used to derive a chronic-duration inhalation MRL for soluble uranium compounds of 0.0003 mg/m^3: concentration adjusted from intermittent to continuous exposure and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

*** Enriched uranium; natural and depleted uranium are without asterisks.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; Cont. = continuous; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observable-adverse-effect level; NPN = nonprotein nitrogen; NS = not specified; RBC = red blood cell; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation

Chemical Toxicity - Acute (≤14 days)

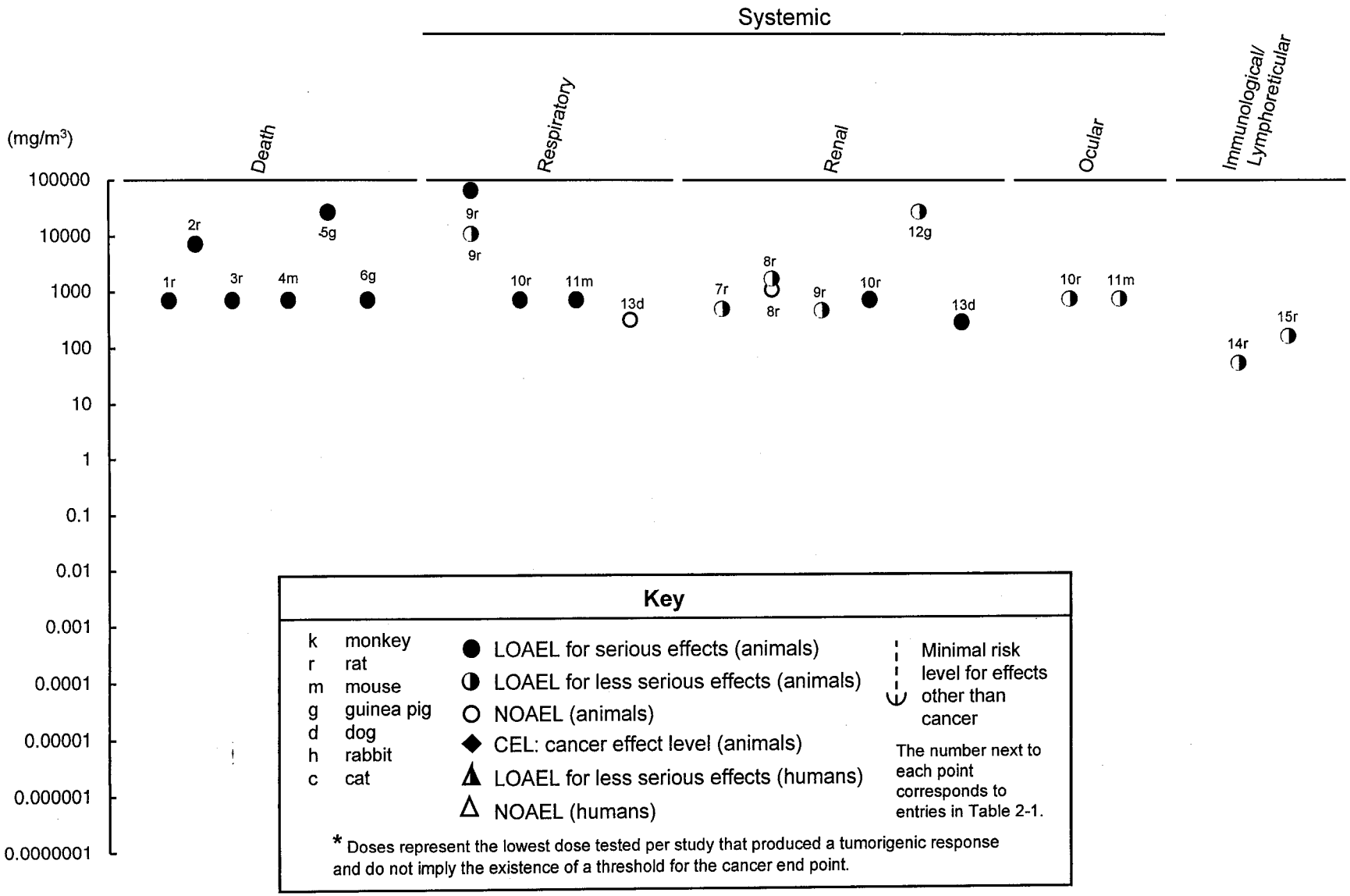


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

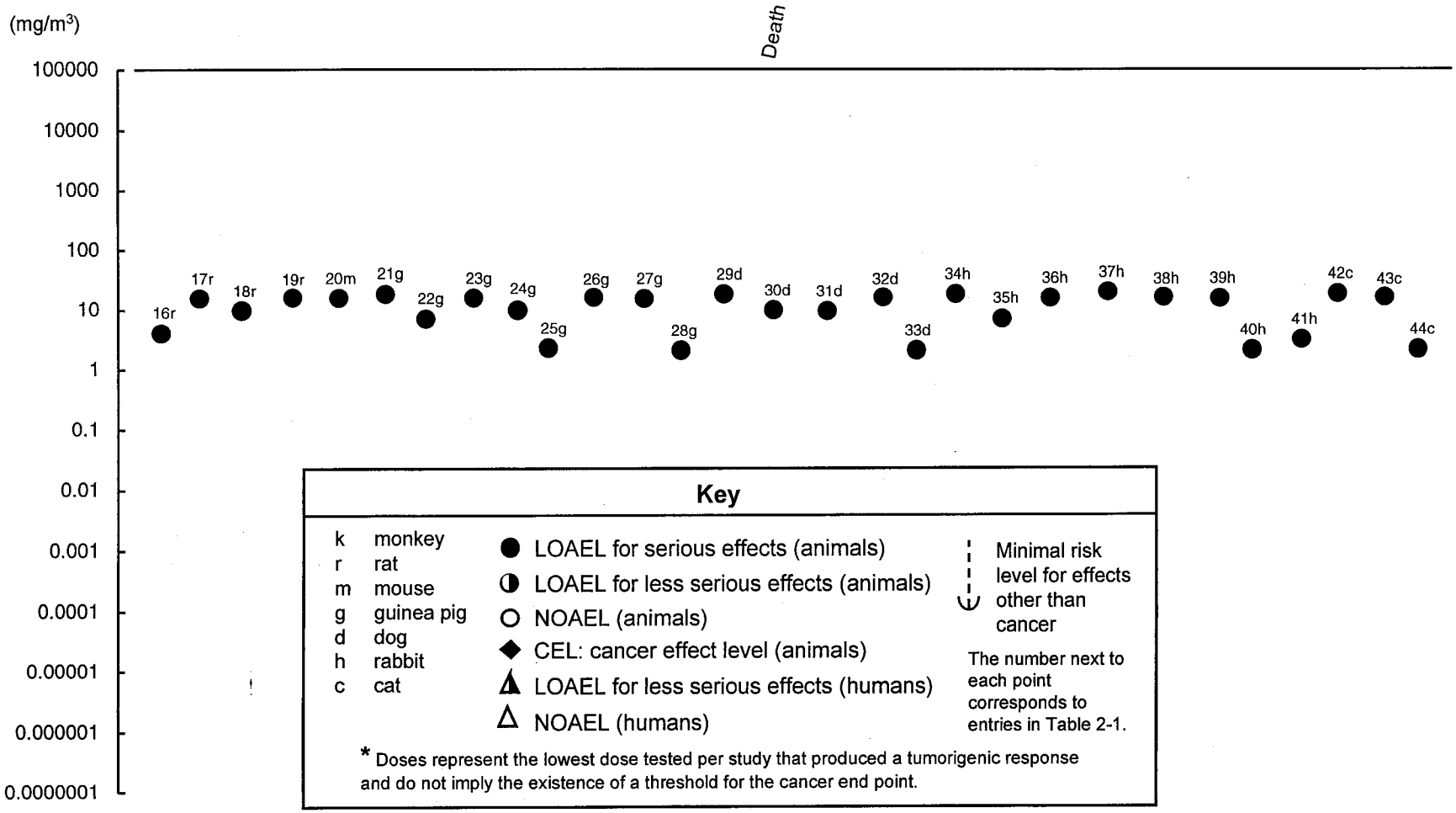


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

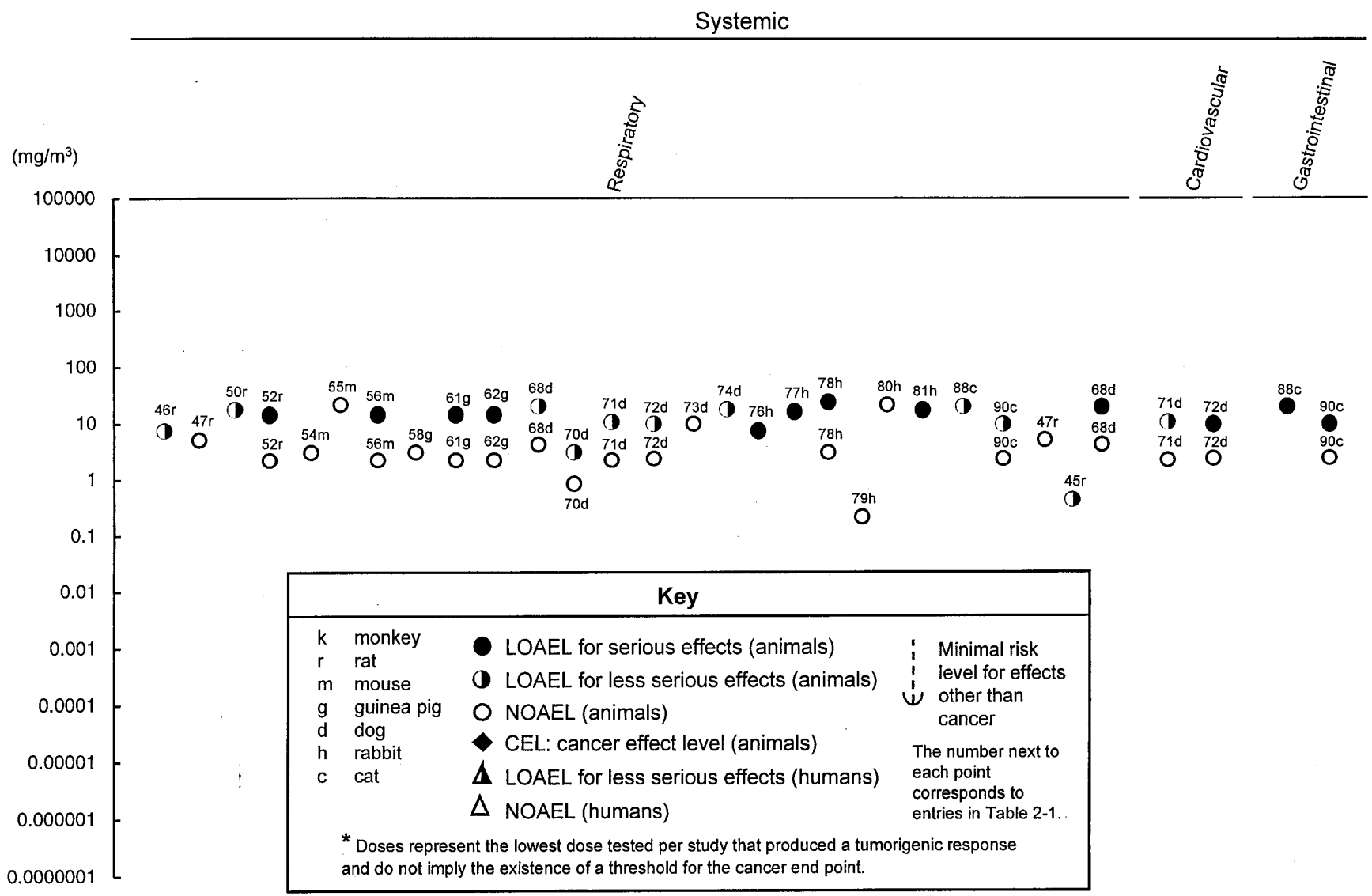


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

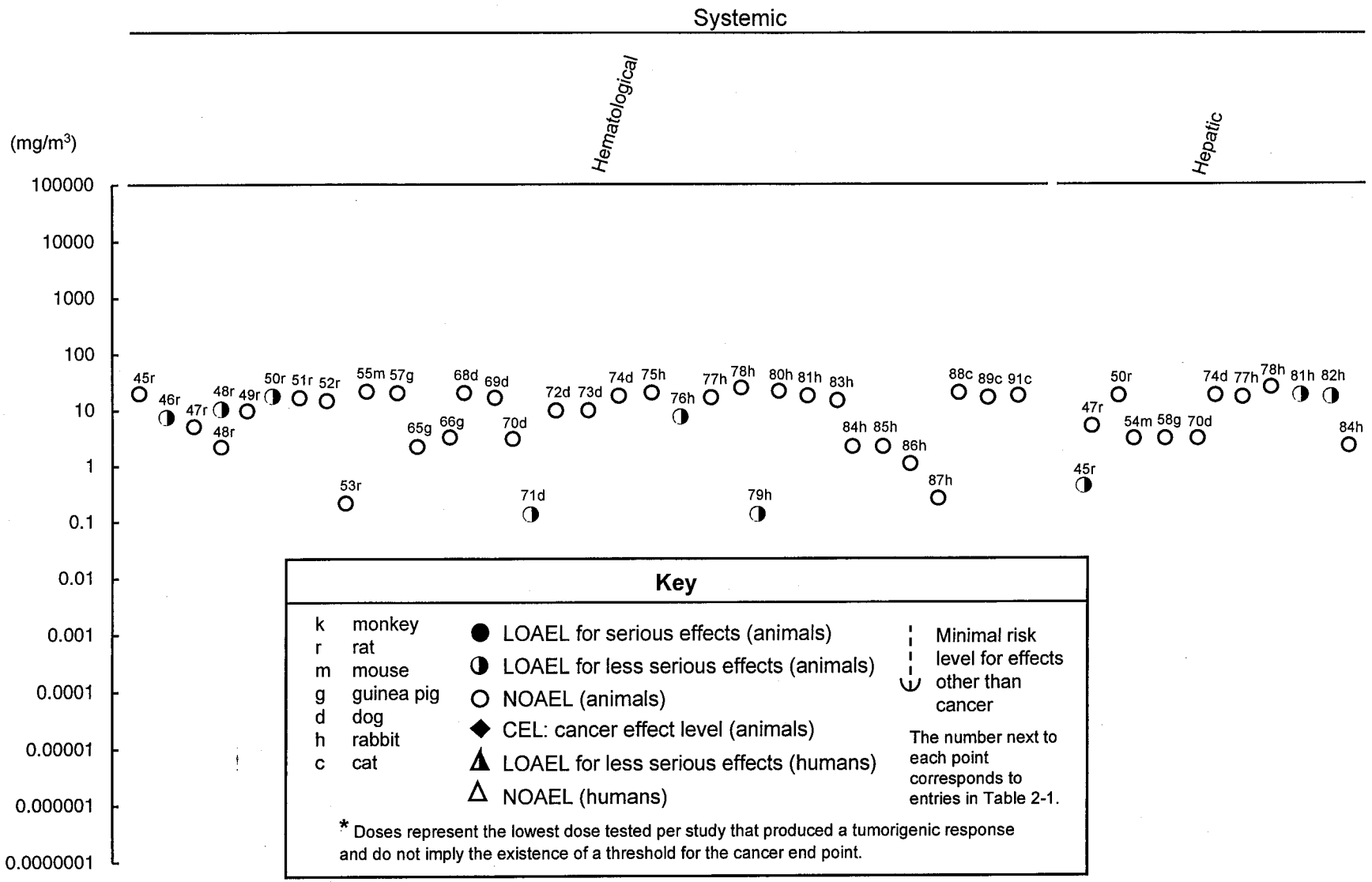


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

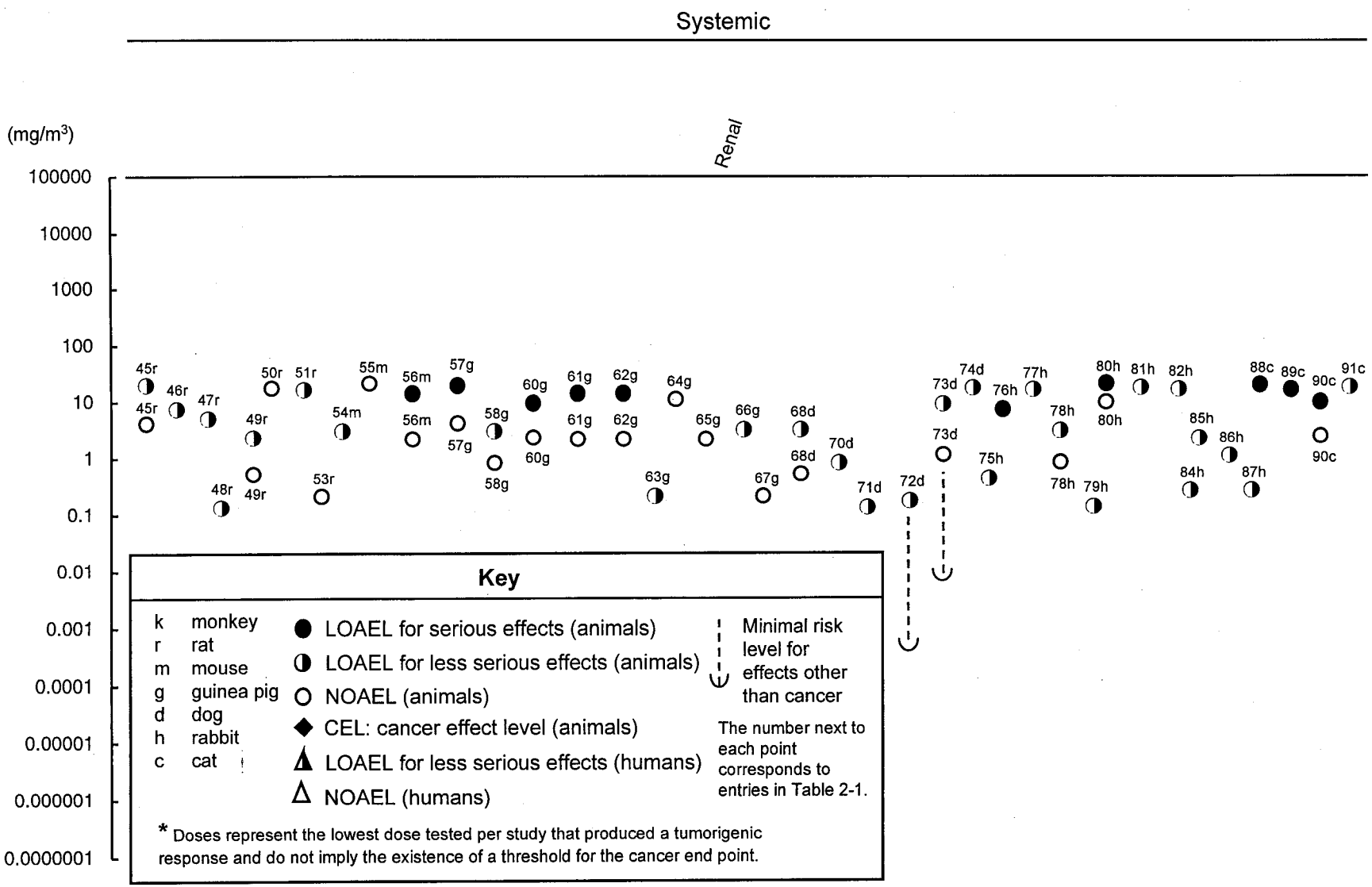


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

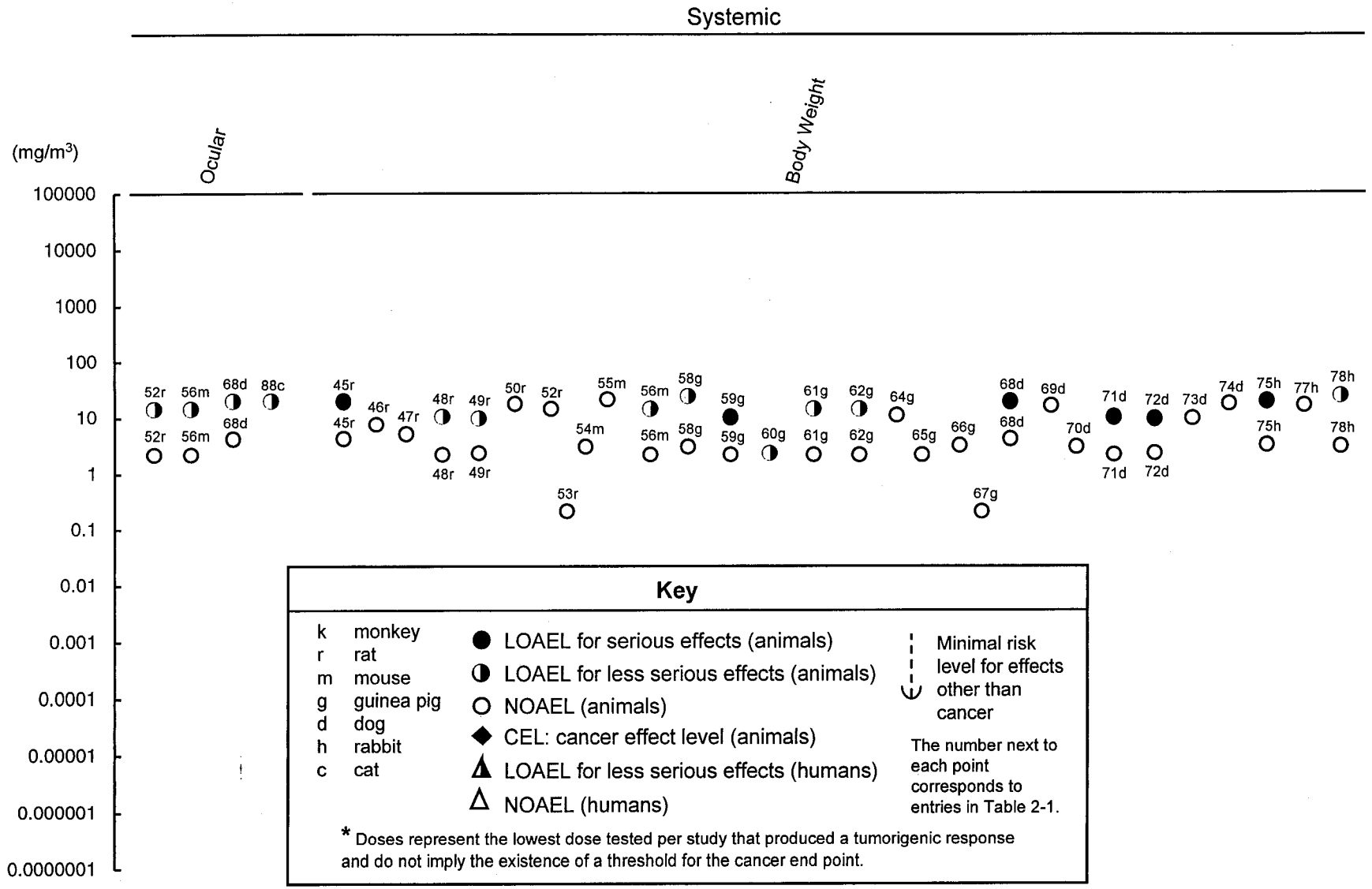


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Intermediate (15-364 days)

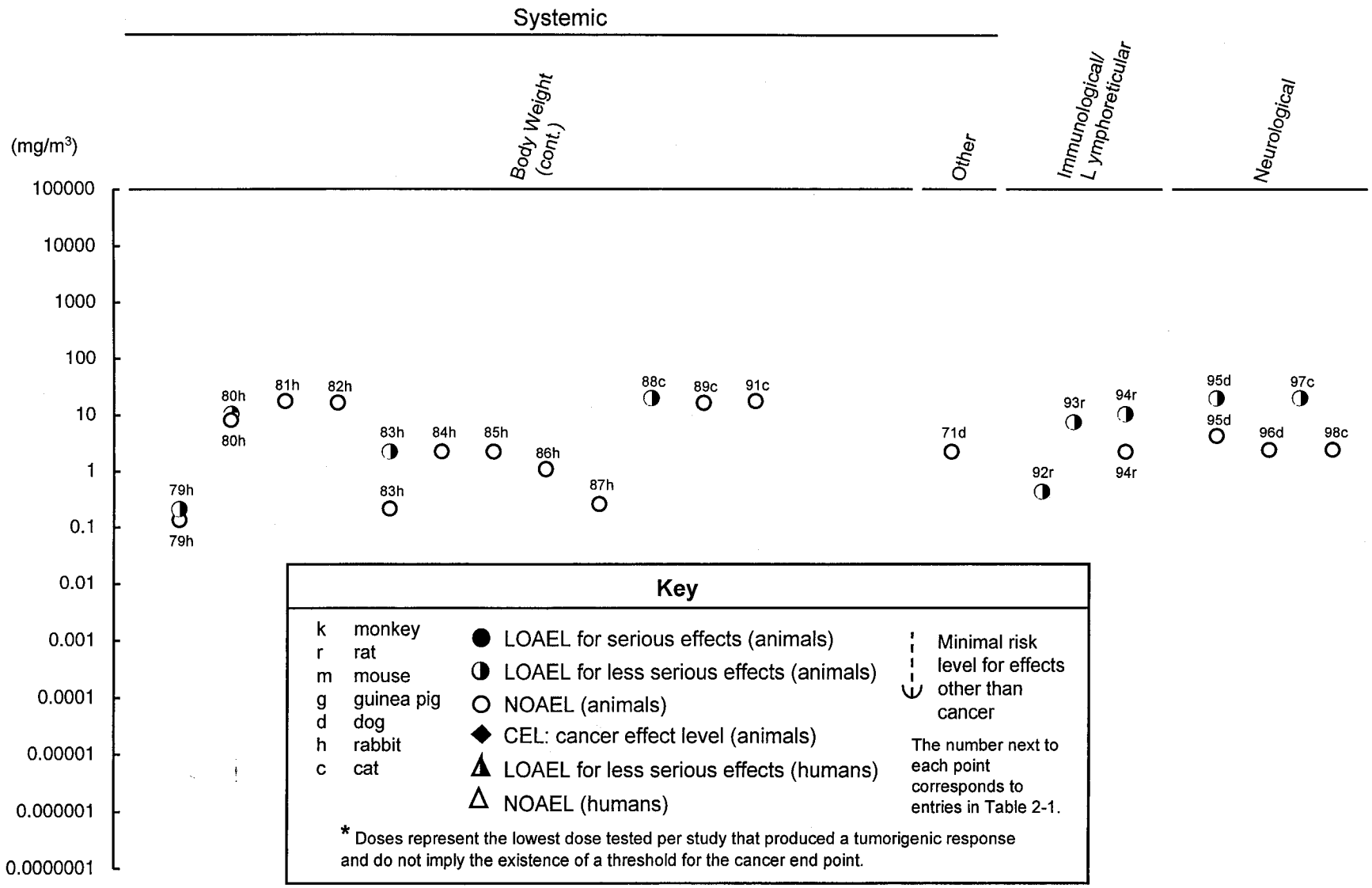


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Chronic (≥365 days)

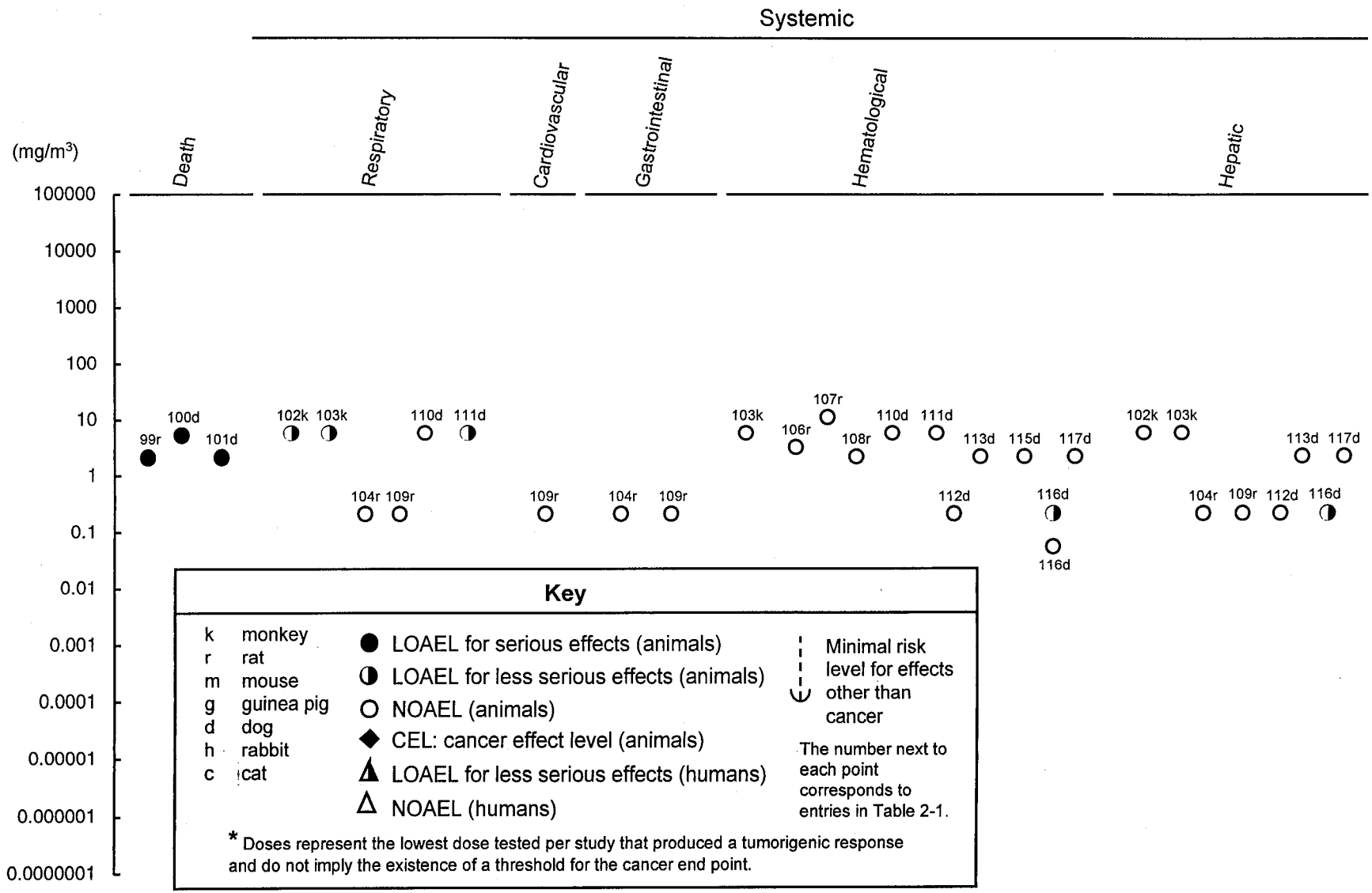


Figure 2-1. Levels of Significant Exposure to Uranium - Inhalation (cont.)

Chemical Toxicity - Chronic (≥365 days)

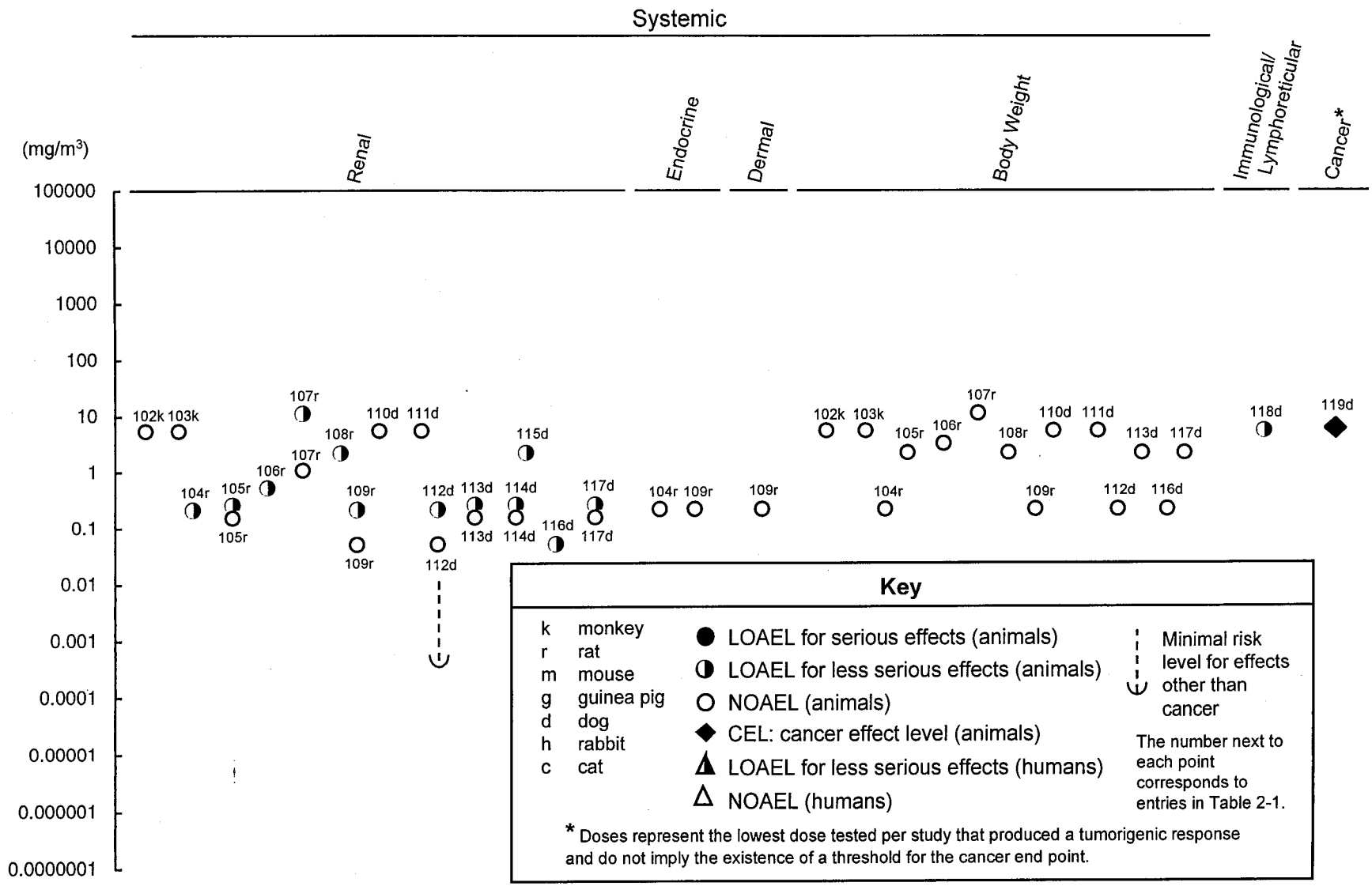


Table 2-2. Levels of Significant Exposure to Uranium - Radiation Toxicity - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (nCi/m3)	LOAEL Less serious (nCi/m3)	LOAEL Serious (nCi/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Rat (Fischer-344)	once 100 min	Resp			5051 M (severe alveolar fibrosis)	Morris et al. 1990 UO2 ***
CHRONIC EXPOSURE							
Cancer							
2	Human	occup				20 rad M (CEL: lung cancer)	Cookfair et al. 1983 *** Uranium dust

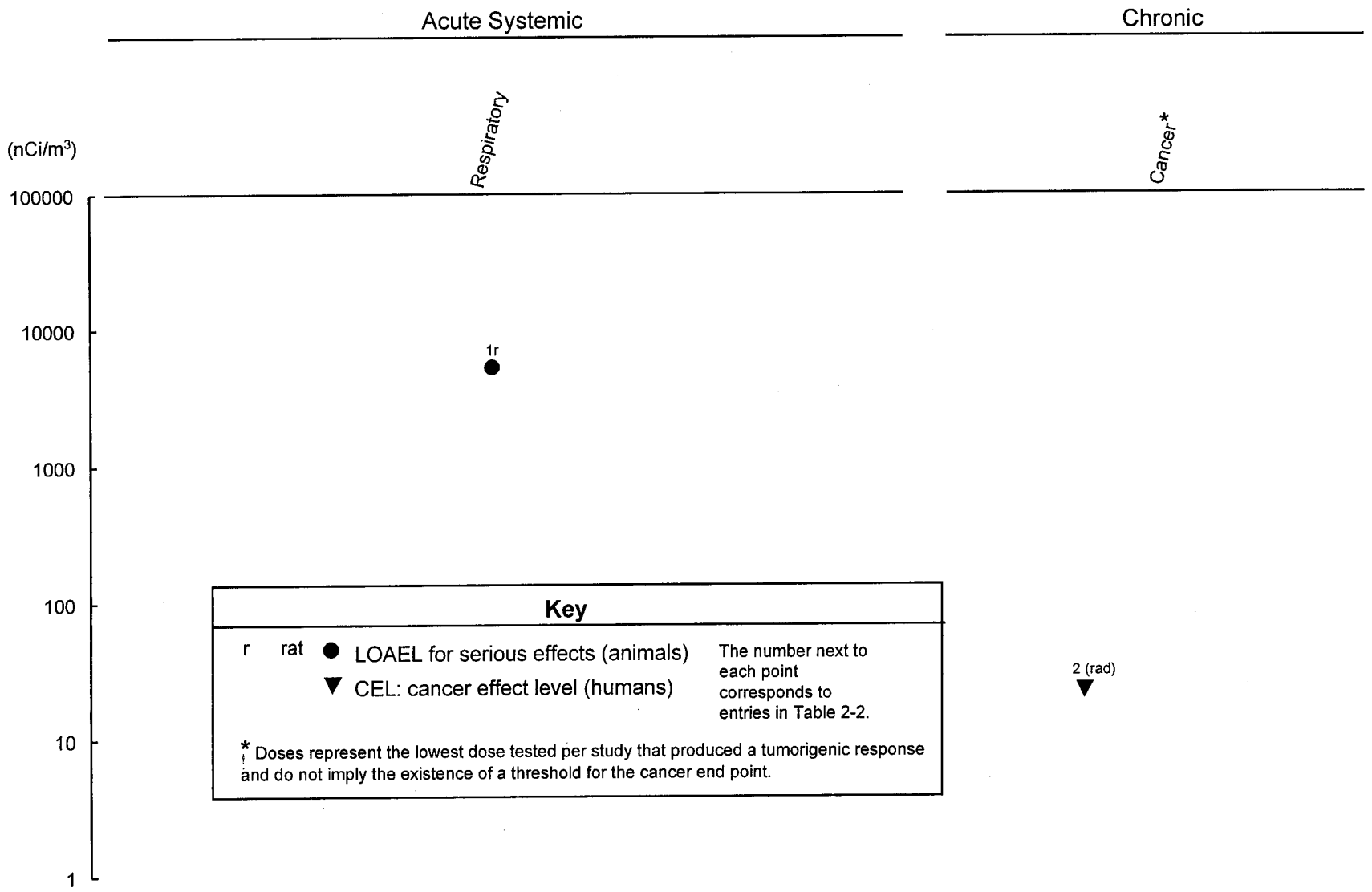
[a] The number corresponds to entries in Figure 2-2.

*** Enriched uranium; natural and depleted uranium are without asterisks.

CEL = cancer effect level; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; occup = occupational; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to Uranium - Inhalation

Radiation Toxicity - Acute (≤14 days) and Chronic (≥365 days)



Respiratory Effects. The hazard from inhaled uranium aerosols, or from any noxious agent, is the likelihood that the agent will reach the site of its toxic action. Two of the main factors that influence the degree of hazard from toxic airborne particles are 1) the site of deposition in the respiratory tract of the particles and 2) the fate of the particles within the lungs. The deposition site within the lungs depends mainly on the particle size of the inhaled aerosol, while the subsequent fate of the particle depends mainly on the physical and chemical properties of the inhaled particles and the physiological status of the lungs.

Small particles (about 2 micrometers [μm] or smaller in diameter) tend to be deposited in the alveoli. The alveoli, frequently called the "deep respiratory tract," form the functional part of the lungs where gas exchange occurs. As the particle size increases, progressively fewer particles penetrate into the deep respiratory tract, and increasingly greater fractions of the inhaled particles are deposited in the upper respiratory tract. The respiratory tract is a system of ducts that starts at the nares and includes the pharynx, larynx, trachea, and a complex series of bronchi and bronchioles that terminate in several thousand alveoli. Three different mechanisms are involved in the removal of particles from the respiratory tract. The first is mucociliary action in the upper respiratory tract (trachea, bronchi, bronchioles, and terminal bronchioles), which sweeps particles deposited there into the throat, where they are either swallowed into the gastrointestinal tract or spat out. The two other clearance mechanisms, dissolution (which leads to absorption into the bloodstream) and phagocytosis (removal by specialized cells in the process), deal mainly with the particles deposited in the deep respiratory tract (respiratory bronchioles, alveolar ducts, and alveolar sacs) (ICRP 1994; NCRP 1997). The less soluble uranium particles may remain in the lungs and in the regional lymph nodes for weeks (uranium trioxide, uranium tetrafluoride, uranium tetrachloride) to years (uranium dioxide, triuranium octaoxide).

In acute exposures, respiratory disease may be limited to interstitial inflammation of the alveolar epithelium, leading eventually to emphysema or pulmonary fibrosis (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992). In studies of the pulmonary effects of airborne uranium dust in uranium miners and in animals, the respiratory diseases reported are probably aggravated by the inhalable dust particles' (the form in which uranium is inhaled) toxicity because most of the respiratory diseases reported in these studies are consistent with the effects of inhaled dust (Dockery et al. 1993). In some of these instances, additional data from the studies show that the workers were exposed to even more potent respiratory tract irritants, such as silica and vanadium pentaoxide (Waxweiler et al. 1983).

The effects of massive acute exposures to uranium in humans, as well as epidemiologic or clinical studies of uranium mine workers chronically exposed to mine atmospheres (containing other noxious agents that include silica, diesel fumes, cigarette smoke, and radon and its daughters), have been investigated. Several epidemiologic studies have reported respiratory diseases in uranium mine and mill workers, who are also exposed to significant amounts of dust and other pulmonary irritants, but not in uranium-processing workers, who are not exposed to these potential aggravants.

Accidental exposure of workers to estimated airborne concentrations of 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) resulted in acute respiratory irritation, which is attributed to the hydrofluoric acid decomposition product. One worker died of pulmonary edema a few hours after the accident (Fisher et al. 1990; USNRC 1986). In another report, 20 men who were seriously injured following accidental exposure to a stream of uranium hexafluoride when a transportation cask ruptured showed signs of pulmonary edema, which also was attributed to hydrofluoric acid. After 3 weeks, most had normal clinical findings and were considered to be in excellent health. A follow-up examination 38 years later on three of the injured workers showed no detectable uranium deposition and no respiratory findings attributable to the exposure (Kathren and Moore 1986). No clinical signs of pulmonary toxicity were found in about 100 uranium-processing workers exposed to insoluble uranium dust at levels of 0.5–2.5 mg U/m^3 for about 5 years (Eisenbud and Quigley 1955). Other reports of workers in the uranium processing industry did not show increased deaths due to diseases of the respiratory system related to exposure to uranium (Brown and Bloom 1987; Cragle et al. 1988; Polednak and Frome 1981; Scott et al. 1972).

A 30-year follow-up study in which ionizing radiation hazard was assessed for a study cohort consisting of 995 workers in a uranium-processing facility that operated between 1943 and 1949 found statistically significant increases in death from all causes. Significantly increased mortality was observed for cancer of the larynx and for pneumonia, but not for lung cancer. The workers were exposed to internal radiation from the inhaled uranium dust, with an upper limit of 1,000 mSv. The data (external radiation badge) for the last 24 months of operation indicated that the highest cumulative external gamma dose for a worker was about 20 mSv. Long-term occupational exposure was evaluated in a subcohort that received 150 mSv/year or more. Because the workers were also exposed to radon-222 (^{222}Ra), chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulfuric acid,

the etiology of the reported laryngeal disease is uncertain (Dupree et al. 1987). An increased incidence of deaths (Standard Mortality Ratio [SMR] =2.29) from obstructive pulmonary disease was found in 4,106 workers in a nuclear fuels fabrication plant who were employed for more than 6 months from 1956 to 1978 (Hadjimichael et al. 1983). However, the overall death rate and rate of all cancers combined were lower than expected. The association of disease with exposure to uranium was not confirmed.

The pulmonary toxicity of uranium compounds varies in animals. Reports of pulmonary toxicity in animals after acute-duration exposure to uranium are limited to experiments with uranium hexafluoride. Gasping and severe irritation to the nasal passages were reported after 10 minute exposures at 637 mg U/mg^3 in rats and mice (Spiegl 1949) and nasal hemorrhage in rats after a 5 minute exposure to 54,503 mg/m^3 (Leach et al. 1984). Uranium hexafluoride promptly hydrolyzes on contact with water to uranyl fluoride and hydrofluoric acid. Thus, the animals were potentially exposed to hydrofluoric acid, a potent toxicant to respiratory tract epithelium, which probably contributed to pulmonary tissue destruction (Leach et al. 1984; Spiegl 1949; Stokinger et al. 1953). In addition, exposure to fluoride ions can result in hypocalcemia, hypomagnesemia, pulmonary edema, metabolic acidosis, ventricular arrhythmia, and death (Meditext 1998).

Intermediate-duration exposure to uranium compounds also caused pulmonary toxicity, particularly when exposure was to uranium hexafluoride. Exposure of rats, mice, and guinea pigs to this compound for 6 hours/day for 30 days at 13 mg U/m^3 resulted in pulmonary edema, hemorrhage, emphysema, and inflammation of the bronchi and alveoli (Spiegl 1949). Milder effects were observed with other uranium compounds in a series of experiments where exposure conditions were similar to those found in the workplace (i.e., 5–6 hours/day, 5–6 days/week). For example, rhinitis was observed in cats and dogs after 30 days exposure to 18 mg U/m^3 as uranium tetrafluoride (Dygert 1949a) and after 5 weeks exposure to 9.2 mg U/m^3 as uranyl fluoride (Rothstein 1949a). Histopathological evidence of toxicity was observed in several studies, including slight degenerative changes in rats and dogs exposed to 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and dogs exposed to 9.5 mg U/m^3 as uranyl nitrate (Roberts 1949). Uranium dioxide and triuranium octaoxide did not cause toxicity (Dygert 1949c; Rothstein 1949b). Carnotite uranium ore did not cause toxicity in mice or guinea pigs, but hemorrhagic lungs were observed in dogs (Pozzani 1949). The species differences may reflect deeper penetration of this material into the dog respiratory tract. Rabbits were more sensitive to respiratory effects of uranium compounds than other species. Severe respiratory effects (pulmonary edema, hemorrhage) were observed in this species with

exposure to 6.8 mg U/m^3 as ammonium diuranate (Dygert 1949b), 15.4 mg U/m^3 as uranium peroxide (Dygert 1949d), 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and 22 mg U/m^3 as carnotite uranium ore (Pozzani 1949). Uranium dioxide at 19.4 mg U/m^3 did not cause respiratory effects in rabbits (Rothstein 1949b).

In chronic-duration exposure tests, a total of 3,100 test animals, including rats, rabbits, guinea pigs, and dogs were exposed to aerosols containing 0.05–10 mg U/m^3 of various uranium compounds for 7–13 months. Histological examination of the lungs revealed no signs of injury attributable to uranium exposure. In chronic-duration exposure tests, no histological damage attributable to uranium exposure to the lungs was observed. There was an absence of any other type of histological damage outside the kidneys (Cross et al. 1981a, 1981b; Stokinger et al. 1985). Dogs exposed to 15 mg/m^3 of carnotite ore dust containing 0.6 mg U/m^3 with a particle size activity median aerodynamic diameter (AMAD) of 1.5–2.1 µm for 1–4 years, 5 days a week, 4 hours a day, showed very slightly increased pulmonary resistance, which may not have been statistically significant. Histological findings included vesicular emphysema, which was present to a lesser degree in control animals. Fibrosis was not noted at this concentration (Cross et al. 1981a, 1982).

Exposure of 200 rats, 110 dogs, and 25 monkeys to 5 mg U/m^3 as uranium dioxide dust for 1–5 years for 5.4 hours a day, 5 days a week did not result in histological damage in the lungs of the dogs or rats. Minimal patchy hyaline fibrosis was occasionally seen in the tracheobronchial lymph nodes of dogs and monkeys exposed for more than 3 years. No atypical epithelial changes were noted (Leach et al. 1970).

Because particles containing insoluble uranium compounds can reside in the lung for years, it is likely that radiotoxicity as well as chemical toxicity can result from inhalation exposure to highly enriched uranium compounds. Radiation effects on tissues from the alveolar regions of the lungs were examined in Albino HMT (Fischer 344) male rats exposed, nose-only, for 100 minutes to an aerosol of to 92.8% ^{235}U-enriched uranium dioxide with a concentration of 2,273 nCi/m^3 (84.1 kBq/m^3) to 5,458 nCi/m^3 (202 kBq/m^3). Increases in the sizes and numbers of lung macrophages and type II[3] cells, the numbers of

[3]Type I cells are alveolar lining cells that are involved with the transfer of substances from the alveolus through the wall to the blood. Type II cells are alveolar cells with two functions: oxidative enzymes for lung metabolism, and the production and secretion of the surfactant coating the alveolar surface.

macrophages and type I cells, and a significant increase in the size of lysosomal granules within the macrophages were reported 8 days postexposure. At 7 days postexposure, 35 of the rats were further exposed to thermalized neutrons at a fluence of $1.0x10^{12}$ neutrons/cm^2 over 2.5 minutes in order to study the combined effects of radiation and chemical toxicity. The radiation dose due to the neutrons and the fission fragments was about 600 rads, which is about 300 times greater than the radiation dose from the uranium dioxide alpha particles. No significant difference was found between the uranium dioxide-only group and those that were subsequently irradiated with neutrons, indicating that the extra radiation exposure caused no immediate pulmonary cellular reaction above that produced by uranium dioxide alone. This finding implies that the observed acute pulmonary effects were due to the metallotoxicity of the uranium dioxide rather than to the alpha radiation from the uranium (Morris et al. 1989). General damage to pulmonary structures, usually noncancerous alveolar epithelium damage of type II cells, can occur upon inhalation of insoluble reactive chemicals such as uranium salts and oxides. The main responses of epithelial cells to chronic injury are hyperplasia, hypertrophy, and transdifferentiation (metaplasia). These changes occur predominantly in proximal acinar regions where chronic injury often causes persistent lining of alveolar spaces by enlarged cuboidal cells that are derived from pre-existing type II cells, nonciliated epithelial cells from adjacent bronchioles, or a mixture of the two.

There is evidence that exposure to highly enriched uranium through inhaled or intratracheally instilled enriched uranium compounds adversely affect the epithelium of the lungs. Severe alveolar fibrosis or metaplasia was found in 72% of the sampled lung tissues from Fischer 344 rats exposed for 100 minutes to an aerosol of 92.8% enriched uranium dioxide at a radioactivity concentration of 5 μCi/m^3 (137 kBq/m^3) (~150 mg U/m^3) to 10 μCi/m^3 (270 kBq/m^3) (~300 mg U/m^3). Extensive lung disease of an unspecified nature was observed only in animals sacrificed at 720 days postexposure. The radioactivity concentration of the mixture was estimated as 1.91 kBq/g (51.6 nCi/mg), and the AMAD of the particles ranged from 2.7 to 3.2 μm (Morris et al. 1990).

In other animal studies, changes suggestive of damage from either radiation or diverse inorganic dust (fibrosis) were reported in lungs and tracheobronchial lymph nodes in Rhesus monkeys exposed by inhalation to 5.1 mg/m^3 (as uranium dioxide) corresponding to a radioactivity concentration of 3.4 nCi/m^3 (126 Bq/m^3) for periods >3 years. Estimated cumulative alpha-radiation tissue doses were >500 rads (5 Gy) for the lungs and 7,000 rads (70 Gy) for the lymph nodes. Similarly exposed dogs also developed slight interstitial and vascular fibrosis of the lungs at lung alpha-radiation tissue doses of 760–1,280 rads (7.6–12.8 Gy) (Leach et al. 1970). The effect on the tracheobronchial lymph nodes in animals exposed for

an additional 2 years ranged from involvement of a single node to complete destruction of all nodes, was dose-dependent, and showed a similarity to changes seen after inhalation exposure to plutonium as ^{238,239}Pu dioxide (Leach et al. 1973). Renal damage was not observed in either dogs or monkeys, but fibrosis was found in monkey lung and both necrosis and fibrosis were found in dog and monkey lymph nodes. It was not clear whether the damage was chemically or radiologically induced, but the magnitude of the radiation doses and the presence of lung and lymph node damage in the absence of renal effects was suggestive to the authors of long-term radiation damage (Leach et al. 1970). However, such degenerative changes in the lungs have also been observed following prolonged exposure to diverse inorganic dust.

For more information about lung effects from plutonium and a review of the hazards associated with alpha-emitting radionuclide exposure, see the ATSDR *Toxicological Profile for Plutonium* (ATSDR 1990e) or Appendix D of this profile.

Cardiovascular Effects. No cardiovascular effects have been reported in humans after inhalation exposure to uranium. No effect on blood pressure or pulse rate was observed in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder were not determined. Electrocardiograms and chest X-rays were normal shortly after the accident and over a 7.5-year follow-up period.

No cardiovascular effects were seen in rats exposed to 0.2 mg U/m^3 (0.13 nCi U/m^3) as uranium hexafluoride for 1 year (Stokinger et al. 1953) or in rats, mice, guinea pigs, and rabbits exposed to 4.8 mg U/m^3 (3.2 nCi U/m^3) triuranium octaoxide for 26 days (Dygert 1949c).

Gastrointestinal Effects. Inhalation exposure to uranium has generally not resulted in gastrointestinal effects in humans although transient effects occurred after one accidental exposure (Zhao and Zhao 1990). On the sixth day after a male worker at a uranium-enrichment plant was accidentally exposed for about 5 minutes in a closed room by inhalation to a high concentration of uranium tetrafluoride (natural uranium) powder, the patient reported nausea and loss of appetite. Air concentration and mean particle size of the powder were not determined. On post-accident day 8, the clinical findings were loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool. On post-accident day 9, all parameters returned to normal. The study gave no indication of particle size for assessing deposition in the upper lung and no indication of whether fecal uranium analysis was undertaken to determine if the noted effects may have

been mediated by the mucocilliary clearance of the uranium tetrafluoride from the lung and its subsequent swallowing to the gastrointestinal tract in accordance with the current ICRP lung model (ICRP 1994) or whether the signs were the result of another intestinal irritant. Gastrointestinal symptoms were not among the clinical signs reported for other workers accidentally exposed to uranium hexafluoride (Eisenbud and Quigley 1955; Moore and Kathren 1985; USNRC 1986).

Dogs, but not other species, appear susceptible to gastrointestinal effects after inhalation exposure to high concentrations of uranium compounds. Vomiting was observed during intermediate-duration exposure to 9.5 mg U/m^3 uranyl nitrate (Roberts 1949), 18 mg U/m^3 uranium tetrafluoride (Dygert 1949a), and to 9.2 mg U/m^3 uranyl fluoride (Rothstein 1949a), It is possible that irritation of the gastrointestinal tract occurred either from clearance of uranium particles from the lungs or ingestion of uranium during these whole-body exposures. Histopathological examination of rat gastrointestinal tissues revealed no changes after 1-year exposures to 0.2 mg U/m^3 uranium hexafluoride or uranium tetrachloride (Stockinger 1953).

Hematological Effects. Inhalation exposure to uranium compounds has generally had no effect, or only minor effects on hematological parameters in both humans and animals. In human studies, no hematological effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder were not determined. Small but significant decreases in the hemoglobin concentration and the mean corpuscular hemoglobin concentration and significant increases in red blood cells counts and mean corpuscular volume were found in uranium miners who had worked for <5–20 years. All values measured were well within the normal range, such that values for individual miners could not be used as an estimate of exposure. No evidence of damage to red blood cell formation was found. The ambient concentration to which these workers had been exposed was not provided in the study (Vich and Kriklava 1970).

A study on the mortality among uranium mill workers found four deaths from lymphatic and hematopoietic tissue effects other than leukemia, while only one was statistically expected among these workers, who were occupationally exposed to uranium dust at airborne levels corresponding to a radioactivity concentration of 0.07 nCi/m^3 (0.1 mg/m^3). However, the authors of this study suggest that this excess may be due to irradiation of the lymph nodes by thorium-230 (^{230}Th) (Archer et al. 1973b). No changes in hematological parameters were observed in humans occupationally exposed to uranium dust at a level of 1.7 nCi/m^3 (63 Bq/m^3 or 2.5 mg/m^3) for 5 years (Eisenbud and Quigley 1955).

Some intermediate-duration animal studies observed a range of hematological changes. Rats exposed to dusts of ammonium diuranate containing 6.8 mg U/m^3 for 6 hours a day for 30 days showed a decrease of 1 million in red blood cell counts and a loss of 4 g of hemoglobin/100 mL of blood (Dygert 1949b). It was not stated whether exposure was for 30 consecutive days or on weekdays only. Rats exposed to airborne uranyl nitrate hexahydrate containing 9.5 mg U/m^3 for 8 hours a day, 5 days a week for 30 exposure days showed decreased numbers of erythrocytes and hemoglobin (measured at 24 hours postexposure and weekly thereafter) (Roberts 1949). Increased percentages of lymphoid cells and myeloblasts in bone marrow were reported at termination in rats exposed to airborne uranium peroxide containing 15.4 mg U/m^3 5 hours a day 5 days a week for 23 days (Dygert 1949d). A 4-week study in rats exposed to airborne uranium as uranium trioxide at a concentration corresponding to 16 mg U/m^3 6 hours a day 6 days a week reported similar findings (significant increases in myeloblasts and lymphoid cells of bone marrow) (Rothstein 1949c). Rabbits and rats exposed to airborne uranium at a level corresponding to a uranium concentration of 0.13 mg/m^3 as uranyl nitrate hexahydrate for 30 days exhibited altered blood function as indicated by decreased fibrinogen during the final week of exposure (Roberts 1949).

In contrast to the above findings, most other intermediate-duration animal inhalation studies with soluble and insoluble uranium compounds found no adverse effects on the blood. In intermediate-duration dosing studies lasting 23–40 days, inhalation exposure to various uranium compounds at the following concentrations produced no harmful effects on hematological parameters: 22 mg U/m^3 as high-grade carnotite uranium ore to rats; 2.8 mg U/m^3 as uranium dioxide or triuranium octaoxide to dogs; 22 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits; 11 mg U/m^3 as uranium tetrachloride to rats; 2 mg U/m^3 as uranium tetrachloride to rabbits; 1 mg U/m^3 as uranium tetrachloride to dogs; 13.2 mg U/m^3 as uranium hexafluoride to rabbits and dogs; 0.1 mg U/m^3 as uranium hexafluoride to dogs; 14.5 mg U/m^3 as triuranium octaoxide to mice; 14.5 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits; 14.5 mg U/m^3 as triuranium octaoxide to guinea pigs and rabbits; 15.4 mg U/m^3 as uranium peroxide to dogs, rabbits, and cats; or 4.8 mg/m^3 as triuranium octaoxide to rats, mice, guinea pigs, and rabbits (Dygert 1949c, 1949d; Pozzani 1949; Rothermel 1949; Spiegl 1949).

In other intermediate-duration exposure studies, inhalation exposures to uranium dioxide dusts containing 1 mg U/m^3 for 30 weeks and 2 mg U/m^3 for 26 weeks in rabbits and guinea pigs, respectively (Stokinger et al. 1953), 19.4 mg U/m^3 for 5 weeks in mice, and 9.2 mg U/m^3 for 5 weeks in dogs and rats had no adverse effects on hematological parameters (Rothstein 1949b). Similarly, exposures to 9.2 mg U/m^3 for

5 weeks to rats and dogs (Rothstein 1949a); 16 mg U/m^3 for 4 weeks to rats, rabbits, cats, and dogs (Rothstein 1949c); and 15 mg U/m^3 as sodium diuranate to rats had no harmful effects on hematological parameters (Rothstein 1949d).

In chronic-duration exposures, dogs exposed to an airborne uranium concentration corresponding to a concentration of 0.2 mg U/m^3 as uranium hexafluoride for 1 year exhibited a lengthening in blood clotting time with a decrease in blood fibrinogen levels (Stokinger et al. 1953). However, hamsters exposed to airborne carnotite uranium ore dust containing 0.7 mg U/m^3 for 16–27 months exhibited no adverse hematological effects (Cross et al. 1981b). Similarly, no changes in hematological parameters were observed in rats, dogs, rabbits, and monkeys exposed to airborne uranium at concentrations ranging from 1 to 5.1 mg U/m^3 for 1–5 years (Leach et al. 1970, 1973; Rothstein 1949b; Stokinger et al. 1953).

Musculoskeletal Effects. No studies were located regarding the chemical or radiation effects of uranium on the musculoskeletal system in humans or animals following inhalation exposure for any duration.

Hepatic Effects. No hepatic effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Air concentration and mean particle size of the powder were not determined. Serum hepatic enzyme levels and liver function tests were within normal limits from the time of the incident through a 3-year follow-up period

Data from the available studies provide equivocal evidence that exposure of animals to uranium has effects on the liver, although the etiology for this effect is not clear. Urinary catalase, a measure of hepatic injury, was significantly increased in rabbits at an inhalation concentration of 0.13 mg U/m^3 8 hours a day, 5 days a week for 30 exposure days (Roberts 1949). A slight decrease in hepatic lactate content was observed in rabbits following exposure to 15 mg U/m^3 as sodium diuranate dust (Rothstein 1949d). Rabbits exposed to an inhalation concentration of 16 mg U/m^3 as uranium trioxide dust for 4 weeks suffered moderate fatty livers in 63% of the animals that died (Rothstein 1949c). Focal necrosis of the liver was observed in rats exposed to an inhalation concentration of 0.4 mg U/m^3 as uranium tetrafluoride for 30 days (Dygert 1949a). In other studies, no changes were found in the liver morphology, histology, or function in the following animals: rabbits exposed to 0.15 or 2 mg U/m^3 as uranyl nitrate hexahydrate for 26 weeks; rats exposed to 14.5 mg U/m^3 as triuranium octaoxide dust for

26 days; rats exposed to 16 mg U/m^3 as uranium trioxide for 4 weeks; mice and guinea pigs exposed to 3 mg U/m^3 as high-grade uranium ore dust for 30 days; and rabbits exposed for 30 days to 22 mg U/m^3 as high-grade uranium ore dust (contains uranium dioxide, triuranium octaoxide, and other potentially toxic contaminants) (Dygert 1949c; Pozzani 1949; Rothstein 1949c; Stokinger et al. 1953).

In chronic-duration exposure studies with animals, an unspecified strain of dogs exposed to ambient air concentrations of 0.05–0.2 mg U/m^3 as uranium hexafluoride for 1 year exhibited increased and persistent bromosulfalein retention, indicative of impaired biliary function, at the 0.2 mg U/m^3 concentration level (Stokinger et al. 1953).

Renal Effects. Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the proximal tubules in humans and animals. However, uranium is a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury) (Goodman 1985). Many of the non-radioactive heavy metals such as lead, cadmium, arsenic, and mercury would produce very severe, perhaps fatal, injury at the levels of exposures reported for uranium in the literature (especially for miners and millers). The negative findings regarding renal injury among workers exposed to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has considered that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either people or animals (UNSCEAR 1993; Wrenn et al. 1985). However, it has been suggested that the renal damage from exposure to high-LET alpha-emitting heavy metals, such as uranium, may be the complementary effect of both the chemical toxicity and the radiotoxicity of these metals (Wrenn et al. 1987).

Several epidemiologic studies have found no increased mortality in uranium workers due to renal disease (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). Also, case studies showed that workers accidentally exposed to high levels of uranium did not suffer renal damage, even up to 38 years postexposure (Eisenbud and Quigley 1956; Kathren and Moore 1986), although the tests for renal damage used in these studies were not very sensitive. A recent comparison of kidney tissue obtained at autopsy from 7 uranium workers and 6 referents with no known exposure to uranium showed that the groups were indistinguishable by pathologists experienced in uranium-induced

renal pathology (Russell et al. 1996). Three of 7 workers and 4 of 6 referents were categorized as abnormal. Uranium levels in the workers kidney tissue (estimated by alpha particle emission) ranged from 0.4 µg/kg to 249 µg/kg. One study on the kidney function of uranium mill workers chronically exposed to insoluble uranium (uranium dioxide) revealed renal tubular dysfunction as manifested by mild proteinuria, aminoaciduria, and a concentration-related clearance of β_2-microglobulin relative to that of creatinine when compared to a referent group of cement workers. Air levels of uranium dioxide were not reported. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the area where insoluble uranium oxide yellowcake was dried and packaged (Saccomanno et al. 1982; Thun et al. 1985), which is typically the second dustiest area of the uranium mill following the ore crushing and grinding station. The data from this study are indicative of reduced reabsorption in the proximal renal tubules.

Delayed renal effects were observed after a male worker at a uranium enrichment plant was accidentally exposed to a high concentration of uranium tetrafluoride powder for about 5 minutes in a closed room. While renal parameters were normal during an initial 30-day observation period, the patient showed signs of nephrotoxicity beginning at post-accident day 68 as indicated by significantly elevated levels of urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and decreased phenolsulfonpthalein excretion rate. These abnormalities persisted through day 1,065 but gradually returned to normal values (Zhao and Zhao 1990). The authors used uranium urinalysis data and a pharmacokinetic model (ICRP 1979) to estimate a kidney dose of 2.6 µg U/g kidney on post-accident day 1.

Renal effects were not observed in another accidental exposure (Fisher et al. 1990) in which 24 of 31 initially exposed workers were followed for 2 years. Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) (USNRC 1986). Initial intakes of workers involved in the accident were estimated from uranium excretion data and ranged from 470–24,000 µg uranium. Maximum uranium concentrations in the kidney were estimated by a kinetic model to be 0.048–2.5 µg U/g tissue (Fisher et al. 1991).

The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurs upon discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949b, 1949c; Spiegl 1949; Stokinger et al. 1953).

The magnitude of uranium intake that causes kidney damage depends on the type of uranium compound to which the animal has been exposed, appearing to depend on its solubility and oxidation state. For example, in dogs and monkeys, exposure to 5 mg U/m^3 as uranium dioxide (insoluble) dust for up to 5 years produced no damage to the kidneys, even 6.5 years after the exposure ceased (Leach et al. 1970, 1973). Similarly, rats and guinea pigs were exposed to #10 mg U/m^3 as uranium dioxide for 1 year without noticeable kidney pathology (Stokinger et al. 1953). Uranium dioxide is relatively insoluble in water and is retained in the lungs longer than the other more soluble uranium compounds (uranium tetrafluoride, uranyl fluoride, uranium tetrachloride, uranium peroxide, uranyl acetate, and uranyl nitrate hexahydrate), thereby causing higher toxicity to the lungs and lower toxicity to distal organs such as the kidney. In contrast, relatively soluble uranium compounds have been shown to cause renal tubular damage in dogs, guinea pigs, rabbits, and rats (Leach et al. 1984; Morrow et al. 1982; Roberts 1949; Stokinger et al. 1953). Apparently, the difference in effect is due to the extent of absorption of uranium deposited in the lungs and, thus, the fraction that eventually gets into the blood. Differences in species susceptibility have also been suggested to be an additional factor.

Renal effects can be produced in animals after acute-duration inhalation exposures to uranium. A 10-minute exposure to 637 mg U/m^3 as uranium hexafluoride produced severe degeneration of the cortical tubules 5–8 days later in rats (Spiegl, 1949). These same effects were observed in dogs 1–3 days after a 1-hour exposure to 250 mg U/m^3 as uranyl fluoride (Morrow et al. 1982). Proteinuria and glucosuria were also observed in rats after 2–10-minute exposures to uranium hexafluoride (Leach et al. 1984).

In intermediate-duration studies with guinea pigs, mice, rats, cats, rabbits, and dogs, inhalation exposures to a variety of uranium compounds were damaging to the kidneys. The effects were compound- and concentration-dependent and ranged from minimal microscopic lesions in tubular epithelium, increased urinary catalase, decreased diodrast (iodopyracet) clearance, and transient increased bromosulfalein retention (for low concentrations) to severe necrosis of the tubular epithelium (for high concentrations) in several species (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). In one of these intermediate-duration inhalation exposure studies, mice were exposed to uranium tetrachloride dust at ambient air concentrations of 0.1, 2.1, or 11 mg U/m^3 for 3–7 hours a day 6 days a week for approximately 30 days. The exposure resulted in severe degeneration and necrosis of the renal-cortical tubular epithelium, and mortality, in the 11 mg U/m^3 group by the third day. At the end of the study, moderate tubular

degeneration was observed in the 2.1 mg U/m^3 group and minimal degeneration in the 0.1 mg U/m^3 group. (Rothermel 1949). In another intermediate-duration study, rats suffered renal injury (of inconsistent severity), which became apparent on or about the 7th day and pronounced by the 25th or 26th day, following inhalation exposure to uranyl nitrate hexahydrate at 0.13, 0.2, 0.9, 2.1, or 9.5 mg U/m^3 daily for 8 hours per day, 5 days a week for 30 days. At 0.9 mg U/m^3, the rats showed significant degenerative changes only in the renal tubules and no changes to the glomeruli. Rats exposed to 0.2 mg U/m^3 exhibited only slight damage to the tubular epithelium of the kidneys. At 0.13 mg U/m^3, slight renal tubular degeneration was observed in 1 of the 3 animals sacrificed after 28 days of exposure. Except for the group receiving no dietary supplement, no significant difference in blood CO_2 values was seen at 14 days of exposure to uranium. Thirty days after the start of exposure, all groups exhibited increased blood nonprotein nitrogen (NPN) levels over 14 day values (maximum 111 mg/mL blood for the unsupplemented diet group). No clinical signs of toxicity were observed at any concentration level (Roberts 1949).

Dogs (of both sexes) exposed to 0.13 mg U/m^3 as uranyl nitrate hexahydrate showed mild inner cortex changes after 10 days of exposure. The dogs were given full body exposures to aerosols with an AMAD assumed to be 1.5–2.1 µm; the average was 1.8 µm (Pozzani 1949). Severe nephritis masked any damage from uranium in one dog sacrificed after 10 days of exposure. The dogs showed a transient elevation in protein excretion between days 9 and 12 of exposure. Increased bromosulfalein retention was observed during the second and fourth weeks of exposure. No alterations to blood NPN or total blood CO_2 were observed. Chloride clearance values, which were initially elevated and then became depressed in one dog, returned to normal 37 days after the beginning of exposure. Catalase and protein excretion increased significantly but returned to normal at the end of exposure. No significant changes in diodrast clearance, inulin clearance, and blood NPN levels were observed. Dogs exposed to 0.9 mg U/m^3 exhibited mild inner cortex and medullary ray degeneration and necrosis with moderate epithelial regeneration. Two of the four showed a steady rise in NPN from the beginning of the experiment until they were sacrificed 12 days later, at which time NPN values were 252 and 356 mg%, respectively. Urinary protein in the dogs significantly increased between the 5th and 24th days. The dogs showed a decrease in inulin clearance during the third week of exposure, with a return toward normal values during the fifth week. There was decreased diodrast clearance throughout the observation period, indicating a severe derangement of the excretory capability for diodrast after 1 week (one dog showed a decrease of 69%). Diodrast clearances returned to normal by days 35–37. Two dogs showed a transient decrease in inulin clearance during the third week, lasting until the fifth week. All four dogs showed a drop in total

blood CO_2, attaining a minimum value between the first and seventh days. The minimum value was generally less than half that of controls, indicating severe acidosis. Glucose tolerance was significantly decreased. Large quantities of protein (400–800 mg%) and sugar were excreted. The greatest excretion occurred during the first 6 days of exposure and decreased thereafter. There was also a decrease in urinary creatinine excretion during the exposure. At the 2 mg U/m^3 exposure level, the dogs did not show highly elevated NPN and blood urea nitrogen (BUN) values during exposure. There were no increases in blood NPN or BUN. All dogs exposed to 9.5 mg U/m^3 had severe renal tubular damage. Four dogs showed renal injury followed by repair when they were sacrificed at the end of the exposure (Roberts 1949).

No treatment-related renal effects were seen in other studies when animals were exposed to uranium compounds by inhalation at concentrations as high as 10 mg U/m^3 (as uranium dioxide) in guinea pigs for 28 weeks, 2 mg U/m^3 (as uranyl nitrate hexahydrate) in guinea pigs for 26 weeks, and 16 mg U/m^3 (as uranyl nitrate hexahydrate) in rats for 4 weeks (Rothstein 1949c; Stokinger et al. 1953).

The nephrotoxic effects of uranium in animals may also include damage to the glomerulus as evidenced by histopathological signs in the kidneys of rats and rabbits exposed to 15.4 mg U/m^3 as uranium dioxide for 23 days (Dygert 1949d) and of dogs exposed to 15 mg U/m^3 as uranyl fluoride for 5 weeks (Rothstein 1949d) and to 16 mg U/m^3 as uranium trioxide for 4 weeks (Rothstein 1949c).

In chronic-duration inhalation studies with rats and dogs, uranium (as uranium tetrachloride, uranium tetrafluoride, uranyl nitrate hexahydrate, or uranium dioxide) exposures as low as 0.05 mg U/m^3 and as high as 10 mg U/m^3 for 1–5 years were damaging to the kidneys. Nephrotoxic effects found in these animals ranged from minimal microscopic lesions in tubular epithelium (for low concentrations) to acute tubular necrosis (for high concentrations) (Leach et al. 1970; Stokinger et al. 1953). In one of these chronic-duration studies, dogs were exposed to ambient air concentrations of 0.05 or 0.2 mg U/m^3 as uranium hexafluoride for 1 year for a total of 1,680 exposure hours. The UF_6 was rapidly hydrolyzed to HF gas and UO_2F_2 fumes, whose AMAD was 0.1 µm. After 10 days in the study, there was evidence of mild tubular injury, which was characterized by desquamation of the epithelium and active regeneration in the proximal convoluted tubule in the inner cortex of the kidneys in 86% of animals exposed to 0.2 mg U/m^3. From the 16th week to the end of the study, regeneration of the tubular epithelium was almost complete, with a few flattened atrophic tubules in the inner zone of the cortex. These mild nephrotoxic effects were also observed in 12% of the 0.05 mg U/m^3 exposed animals. Blood non-protein

nitrogen (NPN) levels were normal (elevated blood NPN levels indicate a decrease in renal filtration capacity, similarly to elevated blood urea nitrogen (BUN)). Observed changes in urinary protein were inconsistent and insignificant (Stokinger et al. 1953).

In another study, dogs of both sexes (9–12 M, 9–13 F) were exposed to concentrations of 0.04, 0.15, 0.25, or 2 mg U/m^3 as uranyl nitrate for 6 hours a day, 5.5 days a week for 1 year. The AMAD of the aerosols was given as 2–5 μm. At the termination of the study, histological and biochemical examinations revealed minimal microscopic lesions in the renal tubules and transient increases in blood NPN in the 0.25 mg U/m^3 concentration-level dogs. Transient increases in blood NPN were also observed at higher concentration levels. There were transient decreases in plasma CO_2, although liver function was normal. No significant weight loss was observed in the dogs (Stokinger et al. 1953).

No treatment-related renal effects were seen when Rhesus monkeys and dogs were exposed to uranium dioxide by inhalation at airborne concentrations as high as 5.1 mg U/m^3 for 1–5 years (Leach et al. 1973). Blood NPN levels were consistently elevated in Rhesus monkeys although no renal histopathology was evident (Leach et al. 1973).

Endocrine Effects. A single study was found that reported on possible effects of uranium on the endocrine system. In this study, no histopathology was seen in the endocrine organs (adrenal, pancreas) in rats given 0.2 mg U/m^3 as uranium tetrachloride for 1 year (Stokinger et al. 1953).

Dermal Effects. No dermal effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Zhao and Zhao 1990). Histopathologic examination of the skin was normal in rats exposed to 0.2 mg U/m^3 as uranium tetrachloride for 1 year (Stokinger et al. 1953).

Ocular Effects. Chemical burns to the eyes were reported in humans after accidental exposure to uranium hexafluoride (Kathren and Moore 1986). Conjunctivitis and eye irritation have also been reported in animals after exposure to uranium hexafluoride (Spiegl 1949) and to uranium tetrachloride (Dygert 1949a). Ocular effects were due to direct contact of the eye with vapor or aerosols.

Body Weight Effects. In general, inhalation of insoluble uranium compounds did not significantly affect body weight in animals. Decreased body weight was observed with the more water-soluble compounds. A 30% decrease in body weight was reported for rabbits exposed to 11 mg U/m^3 as uranium tetrachloride dust for 35–40 days. Mice and guinea pigs experienced unspecified weight loss and 13% weight loss, respectively, following exposure to 13 mg U/m^3 as uranium hexafluoride for 30 days. Rabbits suffered 12% weight loss following exposure to 0.2 mg U/m^3 as airborne uranium hexafluoride for 30 days (Spiegl 1949). Mild to severe weight loss was observed in several species during exposure to uranyl nitrate hexahydrate (Roberts 1949). Rabbits lost 22% of their body weight during a 30 day exposure to 0.9 mg U/m^3, dogs and cats lost approximately 25% of their body weight during a similar exposure to 9.5 mg U/m^3. Similar effects were observed with uranium tetrafluoride (Dygert 1949a). Rabbits, rat, cats, and dogs all experienced a greater than 20% weight loss during 30 days exposure to 18 mg U/m^3.

Several intermediate-duration animal inhalation studies with soluble and insoluble uranium compounds found no significant adverse effects on body weight. In short-term intermediate-duration dosing studies lasting from 23 to 40 days, exposure to concentrations at the following levels were without significant effects on body weight: 22 mg U/m^3 as high-grade or carnotite uranium ore to rats, 2.9 mg U/m^3 as uranium dioxide or triuranium octaoxide to dogs, 22 mg U/m^3 as uranium dioxide or triuranium octaoxide to rabbits, 11 mg U/m^3 as uranium tetrachloride to rats, 2.1 mg U/m^3 as uranium tetrachloride to rabbits, 1.1 mg U/m^3 as uranium tetrachloride to dogs, 13 mg U/m^3 as uranium hexafluoride to rabbits and dogs, 0.2 mg U/m^3 as uranium hexafluoride to dogs and guinea pigs, 14.5 mg U/m^3 as triuranium octaoxide to mice, and 4.8 mg U/m^3 as triuranium octaoxide to guinea pigs and rabbits (Dygert 1949c; Spiegl 1949); 15 mg U/m^3 as uranium peroxide to cats and rabbits (Dygert 1949d); 15 mg U/m^3 as carnotite ore (mostly uranium dioxide, triuranium octaoxide) to dogs or 22 mg U/m^3 as carnotite ore to rabbits for 30 days (Pozzani 1949); and 1 mg U/m^3 for 30 weeks to rabbits or 2 mg U/m^3 for 26 weeks to rabbits and guinea pigs (Stokinger et al. 1953). Exposures of rats to 13 mg U/m^3 or of rabbits to 0.1 mg U/m^3 as uranium hexafluoride for 30 days also were without harmful effects (Spiegl 1949).

No effects on body weight were observed after several intermediate-duration dosing studies that lasted 4–5 weeks. These studies researched exposures by the inhalation route as follows: 16 mg U/m^3 as uranium trioxide to rats, rabbits, dogs, and cats; 19 mg U/m^3 as uranium dioxide to mice; 16 mg U/m^3 as uranium dioxide to guinea pigs; 9.2 mg U/m^3 as uranyl fluoride to dogs and rabbits; 2.2 mg U/m^3 as uranyl fluoride to rats; 9.2 mg U/m^3 as uranium dioxide to dogs; 19.2 mg U/m^3 as uranium dioxide to rabbits; 15 mg U/m^3

as sodium diuranate to rats and dogs; and 12 mg U/m^3 as ammonium diuranate to rats for 30 days (8 hours a day, 5 days a week for 6 weeks) (Rothstein 1949a, 1949b, 1949c, 1949d; Stokinger et al. 1953). Hamsters exposed to 0.8 mg U/m^3 as carnotite uranium ore by inhalation for 16–27 months also exhibited no adverse body weight effects (Cross et al. 1981b). Similarly, no changes in body weight were observed in rats, dogs, rabbits, and monkeys exposed to airborne uranium dioxide at 0.1–5 mg U/m^3 for 1–5 years (Leach et al. 1970, 1973; Stokinger et al. 1953).

In chronic-duration studies, exposure to inhalation concentrations of 3 mg U/m^3 as uranium dioxide to monkeys for 5 years produced no significant body weight changes (Leach et al. 1970).

Other Systemic Effects. Several general effects have been attributed to uranium inhalation exposure. In animal studies, dogs exposed to 13 mg U/m^3 as uranium hexafluoride for 30 days exhibited decreased water intake (Spiegl 1949). Reduced food intake was also observed in a 4-week study of rats and mice exposed to 16 mg U/m^3 as uranium trioxide (Rothstein 1949c) and in a 5-week study of rats and mice exposed to 15 mg U/m^3 as sodium diuranate for 6 hours per day, 5½ days per week (Rothstein 1949d).

2.2.1.3 Immunological and Lymphoreticular Effects

Although no studies were located that specifically tested immunological effects in humans following inhalation exposure to uranium, all epidemiologic studies of workers in uranium mines and fuel fabrication plants showed no increased incidence of death due to diseases of the immune system (Brown and Bloom 1987; Checkoway et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981).

Human studies that assessed damage to cellular immune components following inhalation exposure to uranium found no clear evidence of an immunotoxic potential for uranium. No association was found between the uranium exposure and the development of abnormal leukocytes in workers employed for 12–18 years at a nuclear fuels production facility (Cragle et al. 1988). Increases in the number of fatal malignant disease of the lymphatic and hematopoietic tissue reported among uranium mill workers may have been caused by other carcinogens in the work environment such as ^{230}Th. The authors of this report estimated that the workers were exposed to 8–5,100 mg/m^3 (median 110 mg/m^3) uranium mill dust, which contains ^{230}Th as a natural component (Archer et al. 1973b).

In animal studies, rats exposed to dusts of ammonium diuranate containing 6.8 mg U/m^3 for 6 hours a day, 5 days per week for 30 days developed a rise in neutrophils, a decrease in lymphocytes, a moderate fall in the white blood cell count, and a rise in the number of eosinophils (Dygert 1949b). Rats exposed to airborne uranyl nitrate hexahydrate containing 9.5 mg U/m^3 8 hours a day, 5 days a week for 30 exposure days showed an initial increase and a subsequent decrease in the absolute number of lymphocytes and neutrophils (Roberts 1949). Focal necrosis of the spleen and edematous cecal lymph nodes were observed in some rats exposed for 30 days for 6 hours a day to 0.4 and 4 mg U/m^3 uranium tertrafluoride (Dygert 1949a). However, these effects were not observed at 18 mg U/m^3, so the significance of this finding is unclear.

No histopathological changes or accumulation of uranium were evident in the spleens of 110 dogs and 25 monkeys exposed to uranium dioxide dusts (5 mg U/m^3) for 6 hours a day, 5 days a week, 1–5 years and then monitored for up to 6.5 more years. Similar results were seen for rats similarly exposed for 1 year (Leach et al. 1970, 1973). Rats, rabbits, guinea pigs, and dogs exposed to dusts of various uranium compounds for 7–12 months showed no significant histological changes in the lymph nodes and marrow (Stokinger et al. 1953).

There is some evidence from animal studies that exposure to $90% enriched uranium may affect the immune system. Increased macrophage activity, associated with localized alpha tracks in all 5 lobes of the lungs, was seen in Fischer 344 rats exposed to 6,825.5 nCi/m^3 (252 kBq/m^3) through inhalation exposure to enriched uranium dioxide for 100 minutes. The increased activity was evident from days 1–7, 180, 360, 540, and 720 with increases in percent activity of 0.44, 2.15, 19.70, 6.54, and 37.84, respectively. The number and size of macrophage clusters in the lung increased with time postexposure. The radioactive material concentration of the mixture was estimated as 1.91 kBq/mg (51.6 nCi/mg) (Morris et al. 1992). The degree of enrichment was calculated based on this specific activity.

Albino HMT (Fischer 344) male rats were exposed to 92.8% enriched uranium dioxide with a concentration ranging from 2,274.2 nCi/m^3 (84.1 kBq/m^3) to 5,458 nCi/m^3 (202 kBq/m^3). Increases in the sizes and numbers of lung macrophages, with a significant increase in the size of lysosomal granules within the macrophages, were reported 8 days postexposure (Morris et al. 1989).

Dogs exposed to airborne uranium dioxide concentrations of 5.1 mg/m^3 for 1–5 years showed lymph node fibrosis in the lungs. Rhesus monkeys similarly exposed for 5 years showed fibrotic changes in the tracheobronchial lymph nodes. The investigators of these studies concluded that although these effects could not be extrapolated to humans because of the absence of squamous cell carcinomas in the lungs, the changes were suggestive of radiation injury (Leach et al. 1973). However, the morphological changes observed in these studies were similar to observations in humans and animals as a result of exposure to diverse inorganic dust (Dockery et al. 1993).

The highest NOAEL values and all reliable LOAEL values in each species and duration category for immunological effects from chemical exposures by the inhalation route to uranium are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Uranium has not been shown to cause damage to the nervous system of humans by metallotoxic or radiotoxic action following inhalation exposures for any duration. Although no studies were located that specifically tested neurological effects in animals following inhalation exposure to uranium, none of the available studies reported any neurological deficits, such as narcosis, ataxia, or cholinergic signs. Clinical signs in humans following acute exposure to enriched uranium included dizziness and anorexia in one man 6 days after being exposed for 5 minutes to uranium tetrafluoride by inhalation (Zhao and Zhao 1990), but did not include neurological effects in others similarly exposed to uranium hexafluoride (Kathren and Moore 1986; USNRC 1986). Some of the victims were evaluated for as long as 38 years after exposure (Kathren and Moore 1986). In longer-term exposures, epidemiologic studies found no increase in deaths from brain tumors or other neurological diseases that could be attributed to uranium in workers at uranium-processing plants (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988; Polednak and Frome 1981; Reyes et al. 1984). The autopsy reports also did not reveal any other structural pathology of the central nervous system. In a retrospective study, more deaths than expected were found from central and peripheral nervous system diseases (SMR=2.98) in employees in a nuclear fuels fabrication plant. However, the employees were also concurrently exposed to other radiological and chemical agents. The investigators of this study concluded that there was no etiology associated with uranium for the central nervous system and peripheral nervous system diseases (Hadjimichael et al. 1983).

In intermediate-duration animal studies, neurological signs were observed in dogs and cats following inhalation exposure to uranium. On the 13th day of a 30-day study, dogs exposed to 0.5, 3, 4, or 18 mg U/m^3 as uranium hexafluoride gas by inhalation exhibited muscular weakness followed by instability of gait indicative of neurological dysfunction at the highest concentration tested (Dygert 1949a). Anorexia observed in another 8 hours a day, 5 days a week, 30-day study with dogs exposed to an inhalation concentration of 9.5 mg U/m^3 as uranyl nitrate hexahydrate may also have had its origin in neurological dysfunction (Roberts 1949). Similarly, cats exposed to an inhalation concentration of 18 mg U/m^3 as uranium tetrafluoride exhibited unsteady gait on the 7th day in a 30-day study (Dygert 1949a). In 5 week studies (8 hours a day, 5 days a week), dogs and cats exposed to 0.15, 2.2, or 9.2 mg U/m^3 as uranyl fluoride suffered anorexia, severe muscle weakness, and lassitude at the highest concentration tested (Rothstein 1949a). These studies did not assess the potential implications of hydrofluoric acid and fluoride ion exposure.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for neurological effects by the inhalation route to uranium are presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

It is unlikely that inhalation of uranium produces a significant effect on reproductive health. Studies of one human population group (miners) were located which identified a reproductive effect associated with the inhalation exposure of mine air, but the association with uranium compounds was unclear, and the other miner studies observed no reproductive effects. Also, no adverse animal studies were found.

Three studies of one mining population were located that equivocally associated reproductive effects in humans following inhalation exposure to uranium. The studies reported that male uranium miners were found to have more first-born female children than expected, suggesting that uranium's alpha radiation damaged the y-chromosomes of the miners (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981). In addition, it is not certain if the effect described is from exposure to uranium because the workers were also exposed to ^{222}Rn, chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulfuric acid (Dupree et al. 1987).

No animal studies were located that described reproductive effects following inhalation exposure to uranium for any duration of exposure.

2.2.1.6 Developmental Effects

No studies were located which reported effects of uranium on development in humans or animals following inhalation exposures for any duration. The Department of Defense has preliminarily evaluated developmental effects among service members who were actually or potentially exposed to depleted uranium.

2.2.1.7 Genotoxic Effects

No information was located regarding the toxicity of uranium to genetic material in humans or animals following inhalation exposures for any duration.

In human studies, chromosome aberrations have been found in cultured lymphocytes of uranium miners. Miners who had more atypical bronchial cell cytology had more chromosomal aberrations, and some of the aberrations increased with increasing exposure to radon and its decay products. The investigators of the study concluded that this is probably a valid health risk indicator for miner groups, but that it has only limited applicability to individual miners (Brandom et al. 1978). In a similar study with uranium miners in Czechoslovakia, no increased incidence of aberrant DNA or chromosomes attributable to exposure to uranium was found. An increased occurrence of molds (genus *Aspergillus* and *Penicillium*) that produce mycotoxins was observed, suggesting that the inhaled dust was contaminated with these genotoxic microorganisms (Sram et al. 1993). A cytogenic study of men occupationally exposed to uranium found higher levels of chromosome aberrations in the miners than in controls. The investigators of this study concluded that this increase may be attributable to smoking (Martin et al. 1991). In addition, because the miners were also concurrently exposed to chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, diesel smoke, and sulfuric acid in addition to ^{222}Rn, it is unlikely that the effects described in these studies were related in any way to exposure to uranium (Dupree et al. 1987). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The National Toxicology Program (NTP) has not evaluated uranium compounds in rodent cancer bioassays by any route for the potential to induce cancer in humans. However, because uranium emits predominantly high-LET alpha particles, current theories on gene mutation and apoptotic mechanisms of cancer promotion by high-LET alpha radiation suggest a concern for carcinogenesis from uranium's radioactivity (BEIR 1980, 1988, 1990; Otake and Schull 1984; Sanders 1986; UNSCEAR 1982, 1986, 1988) (see Appendix D for a review of the hazards associated with radionuclide exposure).

Although several studies of uranium miners found increased deaths from lung cancer, it is difficult to attribute these cancers to uranium exposure because the miners were also concurrently exposed to known cancer-inducing agents (principally tobacco smoke, radon and its decay products, silica and other dusts, and diesel engine exhaust fumes) and the studies attributed the cancers to exposure to these toxicants and not to uranium exposure (Archer et al. 1973a; Auerbach et al. 1978; Band et al. 1980; Gottlieb and Husen 1982; Kusiak et al. 1993; Lundin et al. 1969; Saccomanno et al. 1971, 1976, 1986; Samet et al. 1984; Whittemore and McMillan 1983). Short-lived radon daughters alone, to which these miners were concurrently exposed, have been shown to increase the risk of developing lung cancer (Saccomanno et al. 1986). In addition, smoking appeared to increase the risk of developing lung cancer from exposure to radon daughters (Band et al. 1980). The available case-control or clinical studies of uranium-processing nuclear plant workers also generally report equivocal findings of cancer induction without establishing any uranium causality (Cookfair et al. 1983; Polednak and Frome 1981).

A review of the morphology of the tumor types induced in the lungs of rats and humans by radiation identified bronchoalveolar adenoma and bronchoalveolar carcinoma, papillary adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and hemangiosarcoma. All the tumor types originated from the alveolar parenchyma region of the lungs. Of these tumor types, squamous cell carcinomas are most often associated with radiation exposure. In irradiated rats, the squamous cell carcinomas are less well differentiated and decidedly more locally invasive. Although cystic squamous tumors do occur after irradiation, the wall of these tumors is less differentiated. The pathogenesis of the radiation-induced squamous tumors appeared to be different from that of chemically induced tumors. The one common feature of the two tumor types may be chronic injury to alveolar type II cells (Hahn 1989).

Squamous cell metaplasia was the predominant aberrant cell type found in many of these cases. Squamous cell metaplasia is found in the young and old and does not always represent a benign-to-malignant process. More frequently, a nonspecific bronchial epithelial reaction develops, and this reaction is readily reversible with the disappearance of the toxic, infectious, or inflammatory factors that caused it. Although, squamous cell metaplasia may develop into neoplasia, patients with neoplasia also shed a variety of metaplastic squamous cells. In a study of 120 uranium miners who died from primary cancer of the lungs, squamous cell metaplasia progressed over time and developed into neoplasia of the lungs in 15–20 years (Saccomanno et al. 1976, 1982). However, a study that reviewed efforts to test uranium miners concluded that radon-progeny exposure may not cause any cell type of lung tumor other than the so-called small-cell (oat cell) carcinoma. The incidence of oat cell cancer of the lungs has decreased over the last 20 years and currently accounts for slightly more than 22% of developing neoplasia in uranium miners (Saccomanno et al. 1982).

An excess of lung cancers has been found in underground uranium miners from the Grants, New Mexico, area. Of 3,055 miners who worked for at least one year prior to 1971, a total of 58 died of lung cancer by the middle of 1985. Of the 43 cancers which had been examined histopathologically, 27 (63%) were small-cell, 14 (33%) were epidermoid, 1 (2%) was adenocarcinoma, and 1 (2%) was large-cell. These mortality data could not be related to the total radon exposure; radon exposure data for the individual miners was complete since 1967, but only mine-average concentrations had been determined for the period prior to that time (Samet et al. 1986) The radon concentration in mine air is measured in working levels (WL), where 1 WL = 100 pCi/L Rn in equilibrium with its daughters, and the total exposure to radon is measured in WLM s where 1 WLM = 170 WL, or the equivalent of breathing air at a concentration of 1 WL for a period of 170 hours (the typical miner work month). A total of 8,487 miners employed between 1948 and 1980 at the Beaver Edge uranium mine in Saskatchewan, Canada, exhibited significant increase in lung cancer deaths when compared to Canadian male mortality rates (65 in exposed populations as opposed to 34.2 expected [$p<0.05$]). A higher incidence of lung cancer was found in workers exposed to more radon than 5 WLM (46 observed as opposed to 15.8 expected) than those exposed to 0–4 WLM (19 observed as opposed to 18.7 expected). A significant relationship was found between radon exposure and increase of lung cancer (3.3% per WLM and 20.8% per WLM/10^6 person-years). The age at first exposure also had a significant effect on risk; those first exposed before the age of 30 were at lower risk than those first exposed at or after 30 years of age. The authors suggested that exposure to radon daughters was the major factor, and it may be a contributory factor to lung cancer in

nonsmokers in the general population (Howe et al. 1986). The frequency of squamous cell cancer increased, relative to other types, with increased levels and durations of smoking, but relative frequency was not affected by radiation exposure. The relative frequencies of small-cell cancer and adenocarcinoma from radiation exposure were less affected by smoking (Archer et al. 1973a; Land et al. 1993; Saccomanno et al. 1988).

Histological examination of lungs from seven underground male uranium miners (ages 52–73) who had cancer and who also had been routinely exposed to radon daughters and other potential carcinogens in the mine environment showed elevated concentrations of ^{238}U and ^{234}U. Four of the seven lungs had squamous cell carcinoma, one had a carcinoma in the left upper lobe, one had carcinoma of the ascending colon, and one had carcinoma *in situ* in the lung. The average radiation dose from uranium was approximately 2 mrad/year ($2x10^{-5}$ Gy/year) compared with more than the 360 mrad ($3.6x10^{-3}$ Gy) dose to the typical U.S. resident from all sources of radiation. Five of the seven miners smoked at least half a pack of cigarettes per day (Wrenn et al. 1983).

A study of miners in northern Ontario with previous inhalation exposure to uranium dust at levels of 0–181 mg U/m^3 (0–121 nCi/m^3 [0–4,487 Bq/m^3]) and a diagnosis of lung cancer found a linear relationship between uranium dose and incidence of lung cancer, but no relationship to uranium exposure was suggested. The latency period was shorter for those employed for a short period of time. Oat cell, anaplastic, small-cell tumors were found more often than squamous, large-cell, poorly differentiated tumors in workers exposed for a short time (Chovil and Chir 1981; Sanders 1986). The frequency of squamous cell cancer in U.S. uranium miners increased, relative to other types, with increased levels and durations of smoking; but relative frequency was not affected by radiation (presumed to be mostly from radon daughters) exposure, which indicated a more likely smoking etiology. However, the relative frequencies of small-cell cancer and adenocarcinoma were less affected by smoking history than by increasing radiation dose. The miners in one of these studies were exposed to a cumulative radiation dose from radon daughters of 40–9,700 WLM (Archer et al. 1973a; Land et al. 1993; Saccomanno et al. 1971, 1982, 1988). A reanalysis study in which sputum samples from 98,181 uranium miners employed on the Colorado Plateau between 1960 and 1980 were collected and used in a cytological analysis for the early detection of cancer development found a significant relationship between exposure to radon decay products and positive cytological diagnosis. No evidence was found linking lung cancer with exposure to uranium. No synergism was seen between age, smoking, and mining exposure, although an additive

effect was seen. No increase in lung cancer was found in men exposed to radon for <300 WLM who also did not smoke (Moolgavker et al. 1993; Saccomanno et al. 1986; Whittemore and McMillan 1983).

A study of 16 Navajo men working as underground uranium miners, who developed lung cancer and were admitted to the hospital between February 1965 and May 1979, concluded that the lung cancers were attributable to radon and its decay products and not from uranium itself. The mean value of the cumulative radon exposure was 1,140 WLM. The authors noted that the minimal use of cigarettes among this group of uranium miners was a strong argument that cigarette smoking was not a major factor in the lung cancers of uranium miners (Gottlieb and Husen 1982). Evaluation of the incidence of bronchiogenic carcinoma in 3,699 Canadian uranium workers employed between 1942 and 1960 found a statistically significant association between inhalation exposure to mine dust and the development of lung cancer (6 of 1,825 surface workers and 16 of 1,874 underground workers). The authors of this study indicated that the workers employed underground for 5 years were generally older than the other groups, which may have contributed to the increase in lung cancer (Grace et al. 1980). In addition, the miners were exposed to greater amounts of airborne radon radioactivity, a known cancer inducer, than airborne uranium radioactivity. Therefore, the lung cancers may be more appropriately attributed to the radioactivity of airborne radon and its short-lived decay products.

A number of case-control studies of uranium-processing nuclear plant workers failed to provide an unequivocal link between the development of lung cancers by workers and uranium exposure because the workers were concurrently occupationally exposed to other radioactive sources, including thorium, tritium, fission products, iodine, activation products, and transuranic products such as americium, curium, californium, and plutonium (Cragle et al. 1988). In one of these case-control studies, a significant increase in the incidence of leukemia deaths was found among employees of a facility exposed to a mean cumulative gamma radiation dose (mostly external) equivalent of 920 mrem (9.2 mSv). In the same study, no increase in death from lymphopoietic and lung cancers was found among the 9,860 male employees of the nuclear fuels production facility who had been occupationally exposed to uranium and other radioactive sources for 90 days to 15 years (Cragle et al. 1988). Another case-control study of male workers who died from lung cancer also could not establish an association between workplace exposure to uranium and lung cancer. The plant operated between 1943 and 1947, separating and enriching uranium for use in atomic bombs. The men were exposed to external gamma radiation lung doses of 0.001–75 rads (0.00001–0.75 Gy) over a period of about 45 years. Although the study found an increase

in the relative risk for those men who were 45 years or older when first exposed, no clear association was established between the development of lung cancer and radiation or uranium exposure (Cookfair et al. 1983; Polednak et al. 1982). An earlier study conducted on the same cohort found no increase in deaths from other causes associated with radionuclides (e.g., bone cancer, leukemia, respiratory or urogenital diseases) (Polednak and Frome 1981). No statistically significant associations were shown between brain tumor deaths and exposure to low levels of uranium dust, plutonium, external radiation, or other occupational risk factors for workers at the Rocky Flats Nuclear Plant in Colorado. None of the workers had body burdens >1 nCi (37 Bq) (Reyes et al. 1984).

The available human studies that investigated the association between the development of bone sarcomas and exposure to uranium failed to produce evidence for the development of bone sarcomas or bone cancers of any type (Archer et al. 1973a; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Polednak et al. 1982; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1988; Samet et al. 1986; Wrenn and Singh 1983).

Development of lymphatic malignancies (other than leukemia) has also been associated with inhalation exposure to materials associated with uranium. In a study of 2,002 uranium millers, 6 deaths from lymphatic malignancies occurred when 2.6 were expected. The latency period was 20 years (Waxweiler et al. 1983). Another study of uranium mill workers found a slight increase in deaths from tumors of the lymphatic and hematopoietic tissue (Archer et al. 1973b). The authors suggested that this finding might not be due to uranium itself, but rather due to irradiation of the lymph nodes by ^{230}Th, a decay product of ^{234}U and a member of the ^{238}U decay chain.

In intermediate-duration animal studies, golden Syrian hamsters exposed to carnotite uranium ore dust (AMAD=1.5–2.1 μm) at a concentration of 19 mg U/m^3 by inhalation for 16 months failed to shown signs of cancer development upon examination of selected tissues including lungs, trachea, liver, kidneys, spleen, heart, and any abnormal tissue. As compared to unexposed controls, the hamsters had significantly more necrotic liver foci and inflammatory lung responses (Cross et al. 1981b).

In the same study, the results of exposure of golden Syrian hamsters for 16–27 months to concentrations of radon progeny, uranium ore dust (0.5 nCi/m^3 [18.5 Bq/m^3]), or a combination of uranium and radon progeny provided evidence that, while prolonged exposure to uranium dust causes inflammation and

proliferative pulmonary changes, inhalation of radon progeny produced bronchiolar epithelial hyperplasia and changes in the alveolar epithelium in hamsters. The authors also concluded that exposure to radon progeny and development of squamous metaplasia and carcinoma were related. The animals had cumulative radon progeny exposures of more than 8,000 WLM. Pulmonary neoplasms occurred in the three radon-progeny-exposed hamsters and in one hamster exposed to a combination of uranium, radon, and radon progeny. Both the hamsters exposed to radon progeny and those exposed to a combination of uranium and radon progeny had a significantly greater incidence of adenomatous proliferative changes in the alveolar epithelium. Uranium ore-exposed hamsters had significantly more necrotic liver foci and inflammatory lung responses than animals from other exposure groups. Specifically, one pheochromocytoma (zero in controls), one melanoma (zero in controls), one hemangioendothelioma (one in controls), two reticulum cell sarcomas (three in controls), and one adrenal cell carcinoma (zero in controls) were seen in animals exposed to uranium dust alone. Two osteosarcomas (zero in controls) were reported in animals exposed to the mixture of uranium ore dust and radon progeny. Four reticulum cell sarcomas (three in controls) and one adrenal cell sarcoma (zero in controls) were also seen in these animals. In animals exposed to radon progeny alone, one undifferentiated sarcoma (zero in controls), three reticulum cell sarcomas (three in controls), and one myelogenous leukemia (one in controls) were observed (Cross et al. 1981b).

In chronic animal studies, analysis of Beagle dogs exposed to 3.4 nCi/m^3 (126 Bq/m^3 or 5 mg U/m^3) uranium dioxide found frank pulmonary neoplasms and atypical epithelial proliferation in 30–46% of the animals. The lung dose was estimated as 600–700 rads (6–7 Gy). Spontaneous tumors in dogs were infrequent, and the incidence found in this study was 50–100 times higher than the expected rate of spontaneous tumors. The authors of the study recommended against the extrapolation of these findings to humans because these glandular neoplasms do not occur frequently in humans (Leach et al. 1973).

Cancer effect levels (CELs) for chemical and radiation inhalation exposure to uranium are shown in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

2.2.2 Oral Exposure

The oral toxicity of uranium compounds has been evaluated in several animal species. The maximal dosage just failing to be lethal for rats in a 30-day feeding test was about 0.5% uranium compound in the diet for the 3 soluble compounds (uranyl nitrate hexahydrate, uranyl tetrafluoride, and uranium tetrachloride) and 20% uranium compound for the 3 insoluble uranium compounds (uranium dioxide, uranium trioxide, and triuranium octaoxide) tested. Some of these studies sweetened the feed to make it edible. No amount of insoluble uranium compounds acceptable to the rat was lethal. Dietary levels of 1–4% soluble uranium compound produced 50% mortality in 30 days. The marked difference in the toxicity of soluble and insoluble uranium compounds is attributable to the ease of absorption and, thus, the dose that reaches the target organs. In general, the water-soluble compounds are more toxic by the oral route because of the greater ease of absorption in the gastrointestinal tract (Domingo et al. 1987, 1989a, 1989b; Goel et al. 1980; Maynard and Hodge 1949; Paternain et al. 1989). In a summary of the oral toxicity in both rats and dogs, several uranium compounds were ordered by relative toxicity as follows: very toxic compounds included uranium tetrachloride, uranium peroxide, and uranyl fluoride; toxic compounds included uranium nitrate hexahydrate, uranyl acetate, ammonium diuranate, sodium diuranate, uranium trioxide, and high-grade uranium ore (carnotite); practically nontoxic compounds were uranium tetrafluoride, triuranium octaoxide, and uranium dioxide (Maynard and Hodge 1949).

2.2.2.1 Death

There are no reports of human deaths from oral exposure to uranium compounds. However, data from animal studies demonstrate that soluble uranium compounds, at very high intake levels, can be lethal to animals through the oral route for all durations of exposure. Uranium compounds at these concentrations are not palatable to animals and require sweetening.

Oral LD_{50} (lethal dose, 50% mortality rate) values of 114 and 136 mg U/kg have been estimated for male Sprague-Dawley rats and male Swiss-Webster mice, respectively, following single gavage administrations of uranyl acetate dihydrate (Domingo et al. 1987). Mortality occurred in pregnant Swiss mice exposed to 0.028, 0.28, 2.8, 28 mg U/kg/day uranium as uranyl acetate dihydrate by gavage in water from day 13 of gestation through postnatal day 21. Two dams in the 2.8 and three in the 28 mg U/kg/day groups died before delivery (Domingo et al. 1989b). Deaths were also reported in mice during the first 10

days of feeding studies with uranyl nitrate (8 of 25 at 925 mg U/kg/day) and with uranyl fluoride (2 of 25 at 452 mg/kg/day) (Tannenbaum and Silverstone 1951)

In 30-day oral studies, oral LD_{50} values for both sexes of rats of an unspecified strain given uranyl fluoride or uranyl nitrate hexahydrate have been estimated as 540 and 1,579 mg U/kg/day, respectively. Oral LD_{50} values were 658 and 1,096 mg U/kg/day as uranium tetrachloride for male and female rats, respectively, in a similar 30-day study (Maynard and Hodge 1949). Another 30-day study, in which male and female rats of an unspecified strain were exposed to oral uranium peroxide doses, oral LD_{50} values were estimated as 827 and 1,103 mg U/kg/day, respectively (Maynard and Hodge 1949). In other intermediate-duration feeding studies with rats, 16% mortality was reported in the animals following dietary administration of 664 mg U/kg/day for 30 days. Most of the animals died from complications of chemically induced kidney damage (Maynard et al. 1953).

Two-year feeding studies with uranyl fluoride, uranyl nitrate hexahydrate, uranium tetrafluoride, and uranium dioxide showed that chronic intake of large amounts of uranium can lead to a decrease in lifespan. The largest daily intake that did not affect longevity in the rat was 81 mg U/kg/day as uranyl fluoride. For the other uranium compounds studied, the maximum daily intakes that did not affect longevity were 1,130 mg U/kg/day as uranyl nitrate, 1,390 mg U/kg/day as uranium tetrafluoride, and 1,630 mg U/kg/day as uranium dioxide. About 18% of the experimental rats survived for the entire 2-year duration of the study, while about 38% of the control animals survived (Maynard and Hodge 1949). Most of the deaths in the available animal studies resulted from chemically induced renal damage.

The LD_{50} values for each species and other LOAEL values for mortality from exposure to uranium by the oral route are presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.2 Systemic Effects

No human studies were located regarding respiratory, endocrine, dermal, ocular, body weight, or other systemic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to uranium compounds.

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (GW)				114 M (LD_{50})	Domingo et al. 1987 UO2(C2H5O)2* 2H2O
2	Rat (NS)	once (F)				664 (16% mortality)	Maynard et al. 1953 UO2(NO3)2*6H2O
3	Mouse (Swiss-Webster)	once (GW)				136 M (LD_{50})	Domingo et al. 1987 UO2(C2H5O)2* 2H2O
	Systemic						
4	Human	once (W)	Gastro		14.3 M (nausea, vomiting, diarrhea)		Butterworth 1955 UO2(NO3)2*6H2O
5	Human	once (IN)	Cardio			131 M (myocarditis)	Pavlakis et al. 1996 UO2(C2H3O2)2*2H2O
			Hemato			131 M (anemia)	
			Musc/skel			131 M (rhabdomyolosis, paralytic ileus)	
			Hepatic		131 M (increased serum ALT, AST, GGT)		
			Renal			131 M (anuria, kidney failure, renal tubule acidosis persisting over 6 months after exposure)	

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
6	Rat (Sprague-Dawley)	once (GW)	Resp	118 M			Domingo et al. 1987 UO2(C2H5O)2* 2H2O
			Hepatic			5.6 M (microhemorrhagic foci)	
			Renal		5.6 M (slight renal dysfunction; minimal focal microscopic lesions in tubular epithelium)		
			Bd Wt		5.6 M (significant weight loss)		
	Neurological						
7	Rat (Sprague-Dawley)	once (GW)				11 M (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos)	Domingo et al. 1987 UO2(C2H3O2)2*2H2O
	Reproductive						
8	Rat (NS)	once (F)				664 (reduced litter size)	Maynard et al. 1953 UO2(NO3)2*6H2O
9	Mouse (Swiss-Webster)	Gd 6-15 (GW)			3 F (maternal reduced weight gain and food consumption; increased relative liver weight)		Domingo et al. 1989a UO2(C2H3O2)2*2H2O
	Developmental						
10	Mouse (Swiss-Webster)	Gd 6-15 (GW)				3 (underdeveloped renal papillae; cleft palate)	Domingo et al. 1989a UO2(C2H3O2)2*2H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
11	Rat (NS)	30 d (F)				541 (LD_{50})	Maynard and Hodge 1949 UO2F2
12	Rat (NS)	30 d (F)				658 M (LD_{50}) 1096 F (LD_{50})	Maynard and Hodge 1949 UCl4
13	Rat (NS)	30 d (F)				827 M (LD_{50}) 1103 F (LD_{50})	Maynard and Hodge 1949 UO4
14	Rat (NS)	30 d (F)				7858 M (100% mortality)	Maynard and Hodge 1949 UO2(C2H3O2)2*2H2O
15	Rat (NS)	30 d (F)				664 (increased mortality)	Maynard et al. 1953 UO2(NO3)2*6H2O
16	Mouse (Swiss-Webster)	30 d 1x/d (G)				2.8 F (10% mortality)	Domingo et al. 1989b UO2(C2H3O2)2*2H2O
17	Mouse (Swiss)	38-60 d 1x/d (GW)				5.6 (significant increase in offspring mortality)	Paternain et al. 1989 UO2(C2H5O)2* 2H2O
18	Mouse (dba)	48 wk *ad lib* (F)				925 F (24% mortality)	Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
19	Mouse (dba)	48 wk *ad lib* (F)				452 F	(8% mortality)	Tannenbaum and Silverstone 1951 UO2F2
20	Dog (Beagle)	30 d 6 d/wk (F)				15.4	(lethal dose)	Maynard and Hodge 1949 UO2F2
21	Dog (Beagle)	30 d 6 d/wk (F)				63	(lethal dose)	Maynard and Hodge 1949 UCl4
22	Dog (Beagle)	30 d 6 d/wk (F)				386.4	(lethal dose)	Maynard and Hodge 1949 UO4
23	Dog (Beagle)	30 d 6 d/wk (F)				441	(lethal dose)	Maynard and Hodge 1949 UO2
24	Dog (Beagle)	30 d 6 d/wk (F)				5653	(lethal dose)	Maynard and Hodge 1949 U3O8
25	Dog (Beagle)	30 d 6 d/wk (F)				416	(lethal dose)	Maynard and Hodge 1949 UO3
26	Dog (Beagle)	30 d 6 d/wk (F)				237	(lethal dose)	Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
27	Dog (Beagle)	30 d 6 d/wk (F)				188	(lethal dose)	Maynard and Hodge 1949 Na2U2O7
28	Dog (NS)	138 d (F)				95	(lethal dose)	Maynard and Hodge 1949 UO2(NO3)2*6H2O
29	Dog (Beagle)	30 d 6 d/wk (F)				7580	(lethal dose)	Maynard and Hodge 1949 UF4
30	Dog (Beagle)	30 d 6 d/wk (F)				191	(lethal dose)	Maynard and Hodge 1949 (NH4)2U2O7
31	Rabbit (NS)	30 d (F)				14.2	(67% mortality)	Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Systemic						
32	Rat (Sprague-Dawley)	28 d (W)	Resp	35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
			Cardio	35.3 M 40.0 F			
			Gastro	35.3 M 40.0 F			
			Hemato	35.3 M 40.0 F			
			Musc/skel	35.3 M 40.0 F			
			Hepatic	35.3 M 40.0 F			
			Renal	35.3 M	40.0 F (39% increase in serum uric acid)		
			Endocr	35.3 M 40.0 F			
			Bd Wt	35.3 M 40.0 F			
			Other	35.3 M 40.0 F			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Sprague-Dawley)	91 d (W)	Resp	36.73 M 53.56 F			Gilman et al. 1998a UO2(NO3)2*6H2O
			Cardio	36.73 M 53.56 F			
			Gastro	36.73 M 53.56 F			
			Hemato	36.73 M 53.56 F			
			Musc/skel	36.73 M 53.56 F			
			Hepatic		0.06 M 0.09 F (anisokaryosis, vesiculation, increased portal density, perivenous vacuolation and homogeneity)		
			Renal		0.06 M 0.09 F (tubular dilation, apical nuclear displacement, vesiculation, cytoplasmic vacuolation, glomerular capsular sclerosis, interstitial reticulin sclerosis and lymphoid cuffing)		
			Endocr	0.06 M 0.42 F	0.31 M 2.01 F (multifocal reduction of follicular size, incr. epithelial height in thyroid, decr. amount and density of colloid in males only)		
			Bd Wt	36.73 M 53.56 F			
			Other	36.73 M 53.56 F			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
34	Rat (NS)	30 d (F)	Resp	6637					Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Cardio	6637					
			Gastro	6637					
			Hemato	6637					
			Hepatic	6637					
			Renal	3.3	16.6	(minimal microscopic lesions in tubular epithelium)			
			Bd Wt	331			664	(27% reduction in body weight)	
35	Rat (NS)	30 d (F)	Resp	8768					Maynard and Hodge 1949 UCl4
			Cardio	8768					
			Gastro	8768					
			Hemato	8768					
			Hepatic	8768					
			Renal	88	438	(mild to moderate renal changes)			
			Bd Wt	658	877 M	(18% reduction in body weight gain)			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
36	Rat (NS)	30 d (F)	Resp	11033				Maynard and Hodge 1949 UO4
			Cardio	11033				
			Gastro	11033				
			Hemato	11033				
			Hepatic	11033				
			Renal	55	138	(minimal microscopic lesions in tubular epithelium)		
			Bd Wt		55	(unspecified decreased body weight gain)		
37	Rat (NS)	30 d (F)	Resp	10818				Maynard and Hodge 1949 UO2F2
			Cardio	10818				
			Gastro	10818				
			Hemato	10818				
			Hepatic	10818				
			Renal	5.4	27	(minimal microscopic lesions in tubular epithelium)		
			Bd Wt	541	1082	(35% decreased body weight gain)		

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (NS)	30 d (F)	Resp	12342			Maynard and Hodge 1949 UO2
			Cardio	12342			
			Gastro	12342			
			Hemato	12342			
			Hepatic	12342			
			Renal	12342			
			Bd Wt	12342			
39	Rat (NS)	30 d (F)	Resp	7858 M			Maynard and Hodge 1949 UO2(C2H3O2)2*2H2O
			Cardio	7858 M			
			Gastro	7858 M			
			Hemato	7858 M			
			Hepatic	7858 M			
			Renal	786 M	7858 M (minimal microscopic lesions in tubular epithelium)		
			Bd Wt	196 M	786 M (reduced growth)		
40	Rat (NS)	30 d (F)	Resp	11650 M			Maynard and Hodge 1949 UO3
			Cardio	11650 M			
			Gastro	11650 M			
			Hemato	11650 M			
			Hepatic	11650 M			
			Renal	11650 M			
			Bd Wt	1165 M	11650 M (14% reduced growth)		

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Rat (NS)	30 d (F)	Bd Wt			6637 (retarded growth)	Maynard et al. 1953 UO2(NO3)2*6H2O
42	Rat (Sprague-Dawley)	4 wk (W)	Hemato	4.5 M	9 M (5.3 % increased hematocrit, 9% increased mean corpuscular hemoglobin concentration, 7% increased erythrocytes)		Ortega et al. 1989a UO2(C2H3O2)2*2H2O
			Hepatic	2.2 M	4.5 M (28% increased blood glucose; 34% increased SGOT, 32% increased SGPT)		
			Renal		1.1 M (6% increased total plasma proteins)		
43	Mouse (dba)	48 wk *ad lib* (F)	Bd Wt	462 F			Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O
			Other	462 F			
44	Mouse (C3H)	18 wk *ad lib* (F)	Bd Wt	925 F			Tannenbaum and Silverstone 1951 UO2(NO3)2*6H2O
			Other	925 F			
45	Mouse (C3H)	48 wk *ad lib* (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum and Silverstone 1951 UO2F2
46	Mouse (dba)	48 wk *ad lib* (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum and Silverstone 1951 UO2F2

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
47	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	7.7	15.4	(minimal hemorrhagic lesions)			Maynard and Hodge 1949 UO2F2
			Hepatic	7.7	15.4	(fatty infiltration)			
			Renal	7.7			15.4	(moderate degeneration or tubular epithelium)	
48	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	15.4			386.4	(hemorrhage)	Maynard and Hodge 1949 UO4
			Hepatic	15.4	386.4	(mild degeneration)			
			Renal		15.4	(minimal microscopic lesions in tubular epithelium)			
49	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	5653					Maynard and Hodge 1949 U3O8
			Hepatic	2827	5653	(fatty infiltration)			
			Renal		5653	(proteinuria; glucosuria; minimal microscopic lesions in tubular epithelium)			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
50	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	7580	15160	(mild hemorrhage)			Maynard and Hodge 1949 UF4
			Hepatic	7580	15160	(degenerative fatty changes)			
			Renal		3790	(83% increase in blood urea nitrogen; proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
51	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	17.6	441	(slight hemorrhagic lesions)			Maynard and Hodge 1949 UO2
			Hepatic	17.6	441	(slight degenerative changes)			
			Renal	17.6	441	(proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
52	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	83			416	(hemorrhage)	Maynard and Hodge 1949 UO3
			Hepatic	83	416	(slight fatty infiltration)			
			Renal				83	(severe degeneration changes in tubular epithelium)	
53	Dog (Beagle)	138 d (F)	Renal	47	95	(elevated NPN and BUN, proteinuria, glucosuria)			Maynard and Hodge 1949 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
54	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	191					Maynard and Hodge 1949 (NH4)2U2O7
			Hepatic	191					
			Renal		38	(proteinuria, glucosuria; minimal microscopic lesions in tubular epithelium)			
55	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	12			63	(mild hemorrhage)	Maynard and Hodge 1949 UCl4
			Hepatic	63	313	(minimal hepatic lesions)			
			Renal	63			313	(necrosis)	
56	Dog (Beagle)	30 d 6 d/wk (F)	Gastro	188					Maynard and Hodge 1949 Na2U2O7
			Hepatic	37	188	(fatty infiltration)			
			Renal		37	(mild degenerative changes)			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
57	Rabbit (New Zealand)	91 d (W)	Resp	28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O
			Cardio	28.70 M 43.02 F			
			Gastro	28.70 M 43.02 F			
			Hemato	28.70 M 43.02 F			
			Musc/skel	28.70 M 43.02 F			
			Hepatic	28.70 M 43.02 F			
			Renal		0.05[b] M (anisokaryosis, nuclear 0.49 F vesiculation)	0.88 M (interstitial collagen and/or 43.02 F reticulin sclerosis)	
			Endocr	28.70 M 43.02 F			
			Bd Wt	28.70 M 43.02 F			
			Other	28.70 M 43.02 F			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
58	Rabbit (New Zealand)	91 d (W)	Resp	40.98 M			Gilman et al. 1998c UO2(NO3)2*6H2O
			Cardio	40.98 M			
			Gastro	40.98 M			
			Hemato	40.98 M			
			Musc/skel	40.98 M			
			Hepatic		1.36 M (variation in nuclear size, nuclear pyknosis, extensive cytoplasmic vacuolization)		
			Renal		1.36 M (tubular dilation)	40.38 M (glycosuria, proteinuria, anisokaryosis, nuclear vesiculation, interstitial collagen and/or reticulin sclerosis)	
			Endocr	40.98 M			
			Bd Wt	40.98 M			
			Other	40.98 M			
59	Rabbit (NS)	30 d (F)	Renal		2.8 (slight to moderate renal tubular degeneration)		Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Bd Wt	2.8		14.2 (20% decreased body weight)	
60	Rabbit (New Zealand)	91 d (W)	Renal		0.93 M (increased glomerular basement membrane thickness)		McDonald-Taylor et al. 1992 UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
61	Rabbit (New Zealand)	91 d (W)	Renal		0.93 M (tubular debris, interstitial fibrosis, splitting and thickening of basal lamina, increased size of lysosomes and mitochondria)		McDonald-Taylor et al. 1997 UO2(NO3)2*6H2O
	Immunological/Lymphoreticular						
62	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
63	Rat (Sprague-Dawley)	91 d (W)		7.54 M 9.98 F	36.73 M 53.56 F (sinus hyperplasia in spleen)		Gilman et al. 1998a UO2(NO3)2*6H2O
64	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O
	Neurological						
65	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F			Gilman et al. 1998a UO2(NO3)2*6H2O
66	Rat (Sprague-Dawley)	91 d (W)		36.73 M 53.56 F			Gilman et al. 1998a UO2(NO3)2*6H2O
67	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F			Gilman et al. 1998b UO2(NO3)2*6H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
68	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40.0 F				Gilman et al. 1998a UO2(NO3)2*6H2O
69	Rat (Sprague-Dawley)	91 d (W)		36.73 M 53.56 F				Gilman et al. 1998a UO2(NO3)2*6H2O
70	Mouse (Swiss-Webster)	64 d (W)				11.2 M	(significantly reduced sperm counts)	Llobet et al. 1991 UO2(C2H3O2)2*2H2O
71	Mouse (Swiss-Webster)	4-8 wk (GW)		14				Paternain et al. 1989 UO2(C2H3O2)2*2H2O
72	Rabbit (New Zealand)	91 d (W)		28.70 M 43.02 F				Gilman et al. 1998b UO2(NO3)2*6H2O
Developmental								
73	Mouse (Swiss-Webster)	30 d 1 x/d (G)				28	(decrease in litter size on postnatal day 21; decreased day 21 viability index)	Domingo et al. 1989b UO2(C2H3O2)2*2H2O
74	Mouse (Swiss-Webster)	4-8 wk (GW)		6		14	(embryolethality)	Paternain et al. 1989 UO2(C2H3O2)2*2H2O

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
75	Rat (NS)	2 yr (F)				308 (100% mortality)	Maynard and Hodge 1949; Maynard et al. 1953 UO2
76	Rat (NS)	2 yr (F)				135.2 M (6-12% mortality)	Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
						270 F (57% mortality)	
	Systemic						
77	Rat (NS)	2 yr (F)	Hemato	16.6	33 (mild anemia; increased leucocyte count)		Maynard and Hodge 1949; Maynard et al. 1953 UO2(NO3)2*6H2O
			Renal	16.6	33 (minimal microscopic lesions in tubular epithelium)		
78	Rat (NS)	2 yr (F)	Bd Wt	135.2 M		270 M (30% decrease in body weight)	Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
				135.2 F		270 F (29% decrease in body weight)	
79	Rat (NS)	2 yr (F)	Hemato	12341			Maynard and Hodge 1949; Maynard et al. 1953 UO2
			Renal	12341			
			Bd Wt	12341			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
80	Rat (NS)	2 yr (F)	Hemato	10611			Maynard and Hodge 1949; Maynard et al. 1953 UF4
			Renal	1061	10611 (mild renal tubular degeneration)		
			Bd Wt	10611			
81	Dog (NS)	1 yr (F)	Resp	95			Maynard and Hodge 1949 UO2(NO3)2*6H2O
			Renal	47	95 (elevated NPN, BUN; glucosuria, proteinuria)		
			Bd Wt	95			
82	Dog (Beagle)	1 yr (F)	Hemato	31			Maynard and Hodge 1949; Maynard et al. 1953 UCL4
			Renal	6.3	31 (mild glucosuria, proteinuria)		
83	Dog (NS)	1 yr (F)	Renal	8			Maynard and Hodge 1949; Maynard et al. 1953 UO2F2
			Bd Wt	8			

Table 2-3. Levels of Significant Exposure to Uranium - Chemical Toxicity - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
84	Rat (NS)	2 yr (F)				331 M (testicular degeneration)		Maynard et al. 1953 UO2(NO3)2*6H2O

[a]The number corresponds to entries in Figure 2-3.

[b] Used to derive an intermediate-duration oral exposure minimum risk level (MRL) of 0.002 mg/kg/day; adjusted by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for variability among humans)

ad lib = ad libitum; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NPN = nonprotein nitrogen; NS = not specified; Resp = respiratory; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Uranium - Oral

Chemical Toxicity - Acute (≤ 14 days)

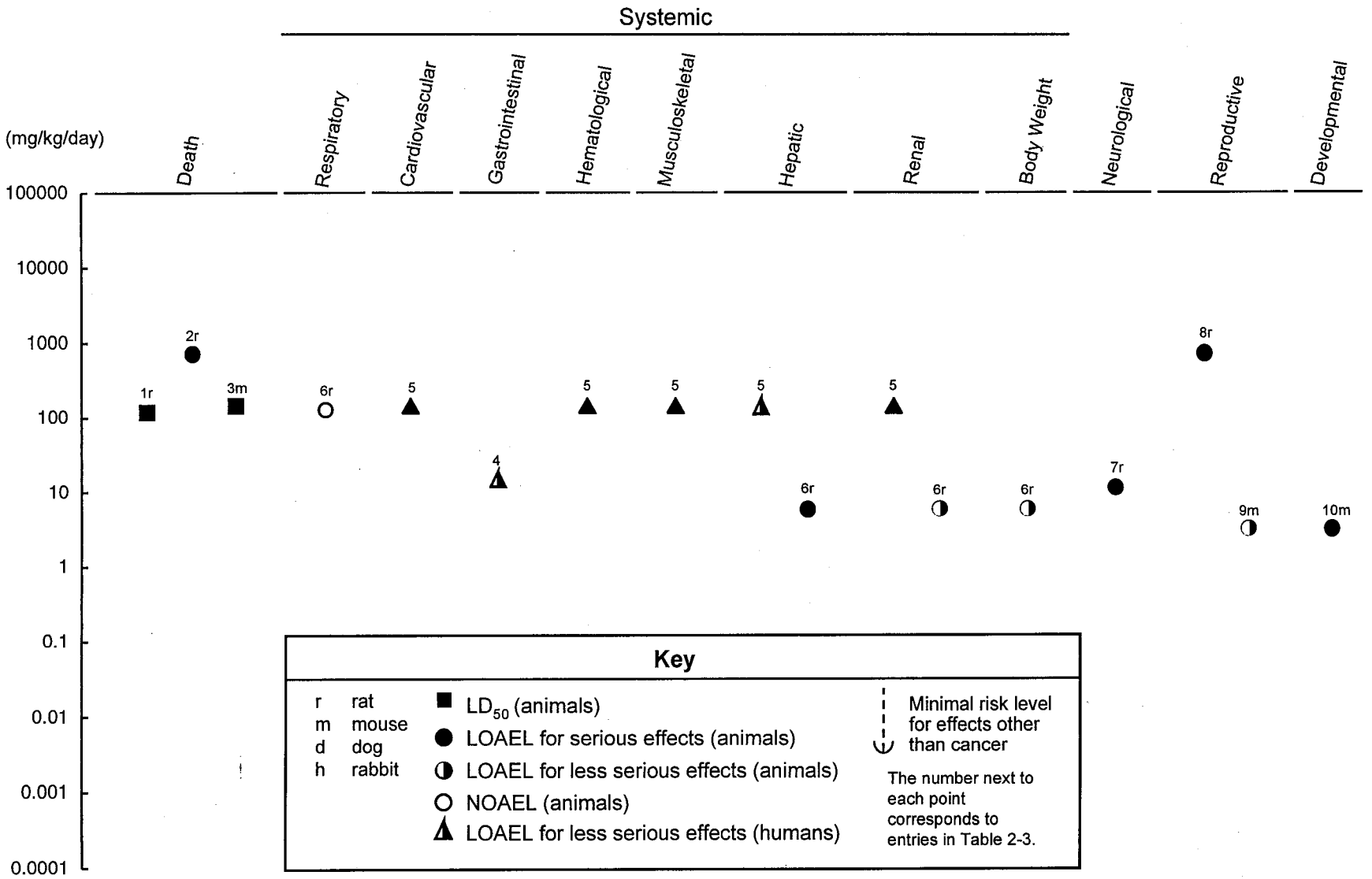


Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

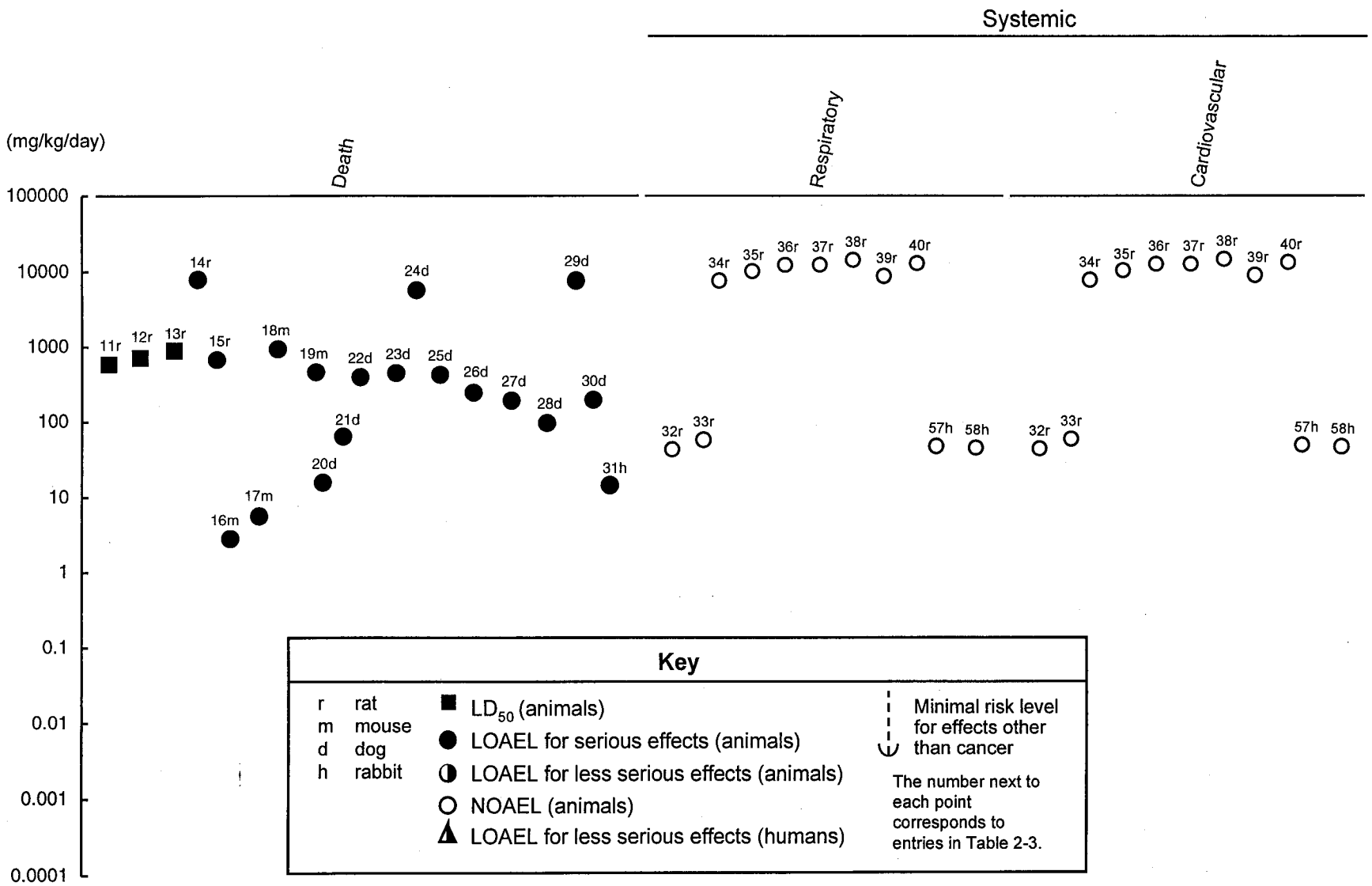


Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

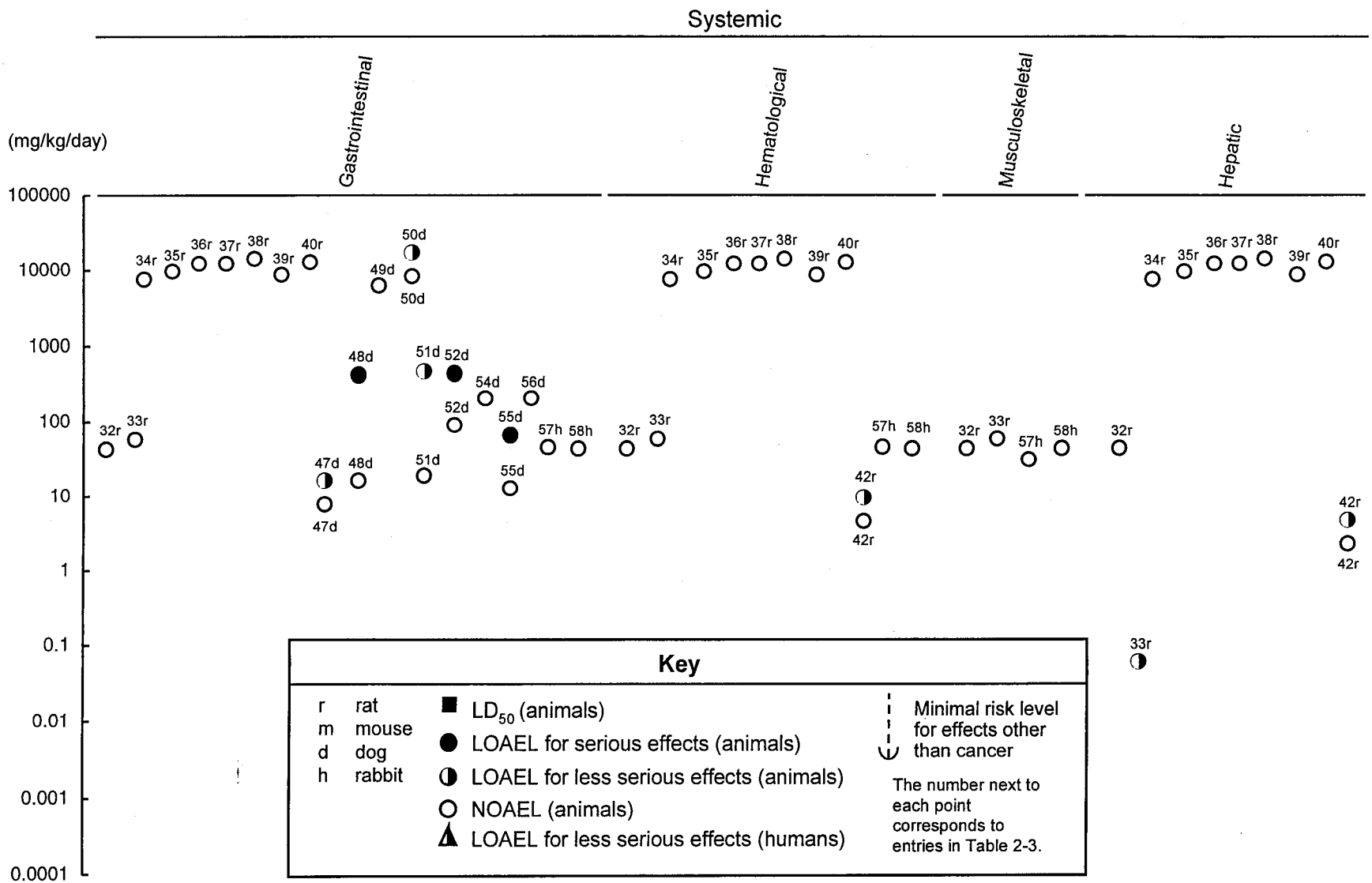


Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

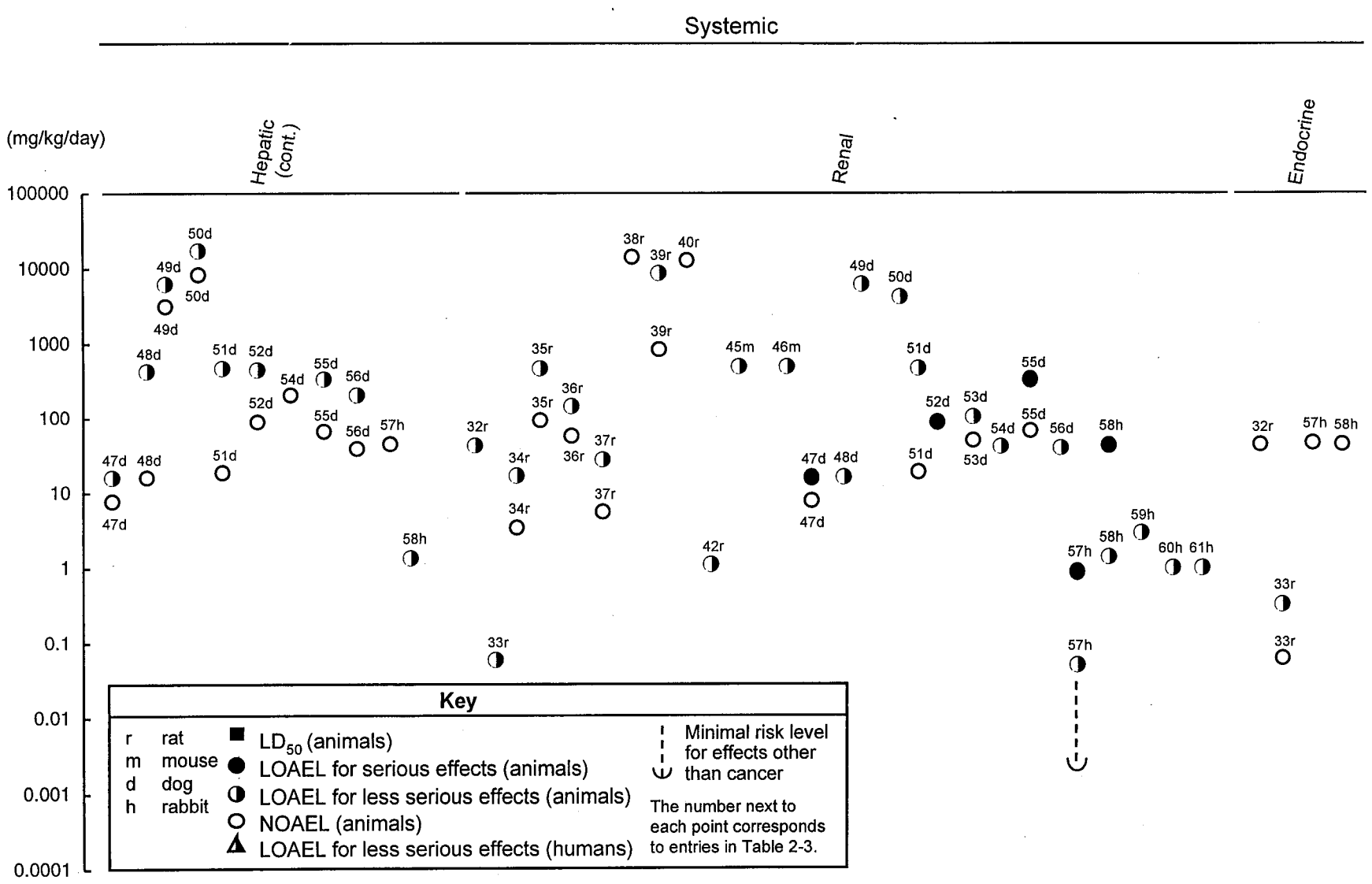


Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Intermediate (15-364 days)

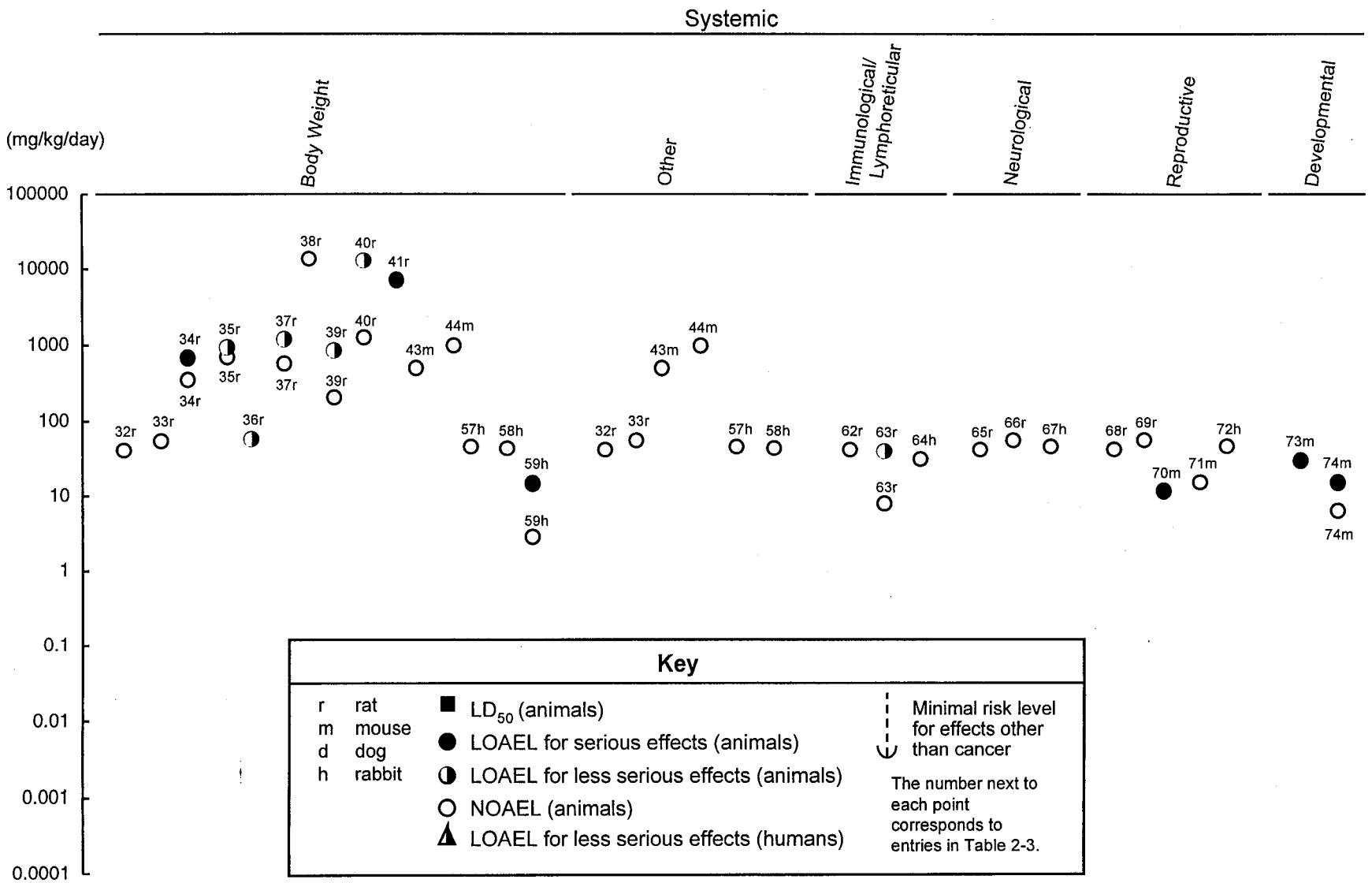
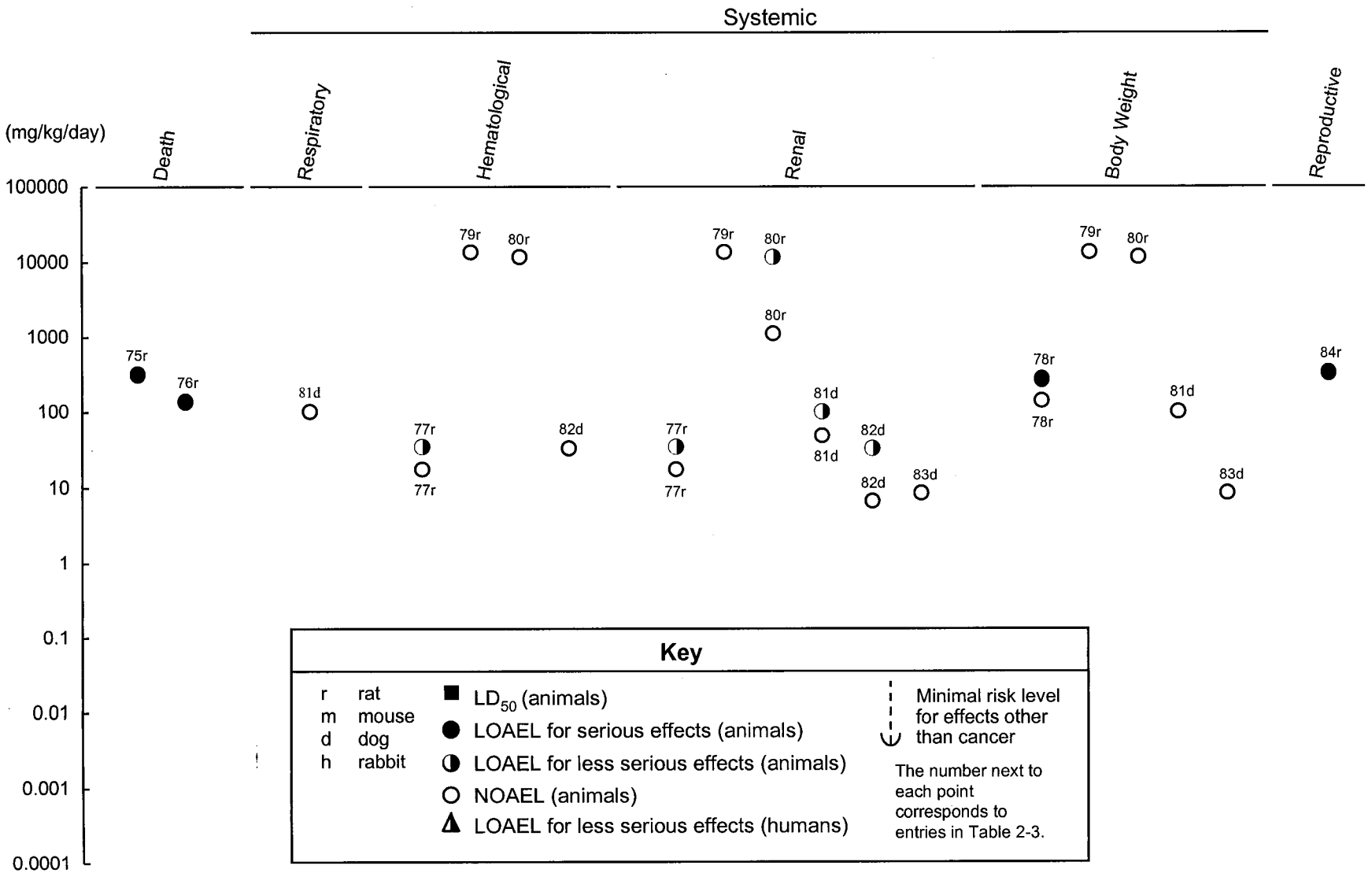


Figure 2-3. Levels of Significant Exposure to Uranium - Oral (cont.)

Chemical Toxicity - Chronic (≥365 days)



Animal data are lacking regarding musculoskeletal, metabolic, dermal, or ocular effects following oral exposure to uranium and its compounds for all durations. Similarly, no animal studies were located on the hematological effects of uranium in animals following acute-duration oral exposure or on the cardiovascular, endocrine, or other systemic effects following acute- or chronic-duration oral exposure. Data exist for the respiratory, renal, and body weight effects following oral exposure of animals to uranium for all durations. However, the existing data on the hematological, cardiovascular, hepatic, and other systemic effects of uranium in animals are limited to acute- or chronic-duration inhalation exposure; data on the gastrointestinal effects are limited to acute-duration exposure.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for systemic effects from chemical exposures to uranium by the oral route are presented in Table 2-3 and plotted in Figure 2-3.

Respiratory Effects. Respiratory effects from oral exposure to uranium are unlikely. In an acute-duration animal study, no adverse effects on the respiratory system were reported in rats given single oral doses of 118 mg uranium per kilogram body weight per day (U/kg/day) as uranyl acetate dihydrate (Domingo et al. 1987).

In intermediate-duration exposures, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in lung weights were noted (Gilman et al. 1998a). In several 30-day dietary studies, no adverse effects on the respiratory system were reported in rats exposed to 6,637 mg U/kg/day as uranyl nitrate hexahydrate, 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as uranium peroxide, 10,611 mg U/kg/day as uranium tetrafluoride, 10,818 mg U/kg/day as uranyl fluoride, 12,342 mg U/kg/day as uranium dioxide, 8.167 mg U/kg/day as uranyl acetate dihydrate, or 11,650 mg U/kg/day as uranium trioxide (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953). Lengthening the duration of exposure to uranium failed to produce detectable lesions in lungs of laboratory animals. Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and were sacrificed. No treatment-related histopathological changes were found in the lungs, and no changes in lung weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the

drinking water (males: up to 28.70 mg/kg/day; females: up to 43.02 mg/kg/day) for 91 days. No treatment-related histopathological changes were found, and no changes in lung weights were noted (Gilman et al. 1998b). Male New Zealand rabbits were also exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, again with no histopathological or organ weight changes found (Gilman et al. 1998c).

In chronic-duration feeding studies, no adverse effects on the respiratory system were reported in 1-year studies of dogs given oral doses of 31 mg U/kg/day as uranium tetrachloride, 3,790 mg U/kg/day as uranium hexachloride, 8 mg U/kg/day as uranyl fluoride, or 4,407 mg U/kg/day as uranium dioxide (Maynard and Hodge 1949; Maynard et al. 1953). In 2-year studies, the respiratory system was unaffected in dogs and rats given 2 mg U/kg/day as uranyl nitrate hexahydrate and in rats given 12,141 mg U/kg/day as uranium dioxide, 664 mg U/kg/day as uranyl nitrate hexahydrate, 10,611 mg U/kg/day as uranium tetrafluoride, or 405 mg U/kg/day as uranyl fluoride (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953).

Cardiovascular Effects. Cardiovascular effects following intake of uranium are unlikely. One case report documented a cardiovascular effect that was possibly related to uranium exposure in a male admitted to the hospital following deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was unremarkable, and decreased cardiac output was consistent with ingestion of benzodiazepam. The patient was reported to have suffered from myocarditis resulting from the uranium ingestion, resolving 6 months after the ingestion (Pavlakis et al. 1996).

The available studies in animals have found no adverse cardiovascular effects following oral exposures for up to 30 days to uranium compounds. In one study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and sacrificed. No cardiac histopathological changes were found, and no changes in heart weights were noted (Gilman et al. 1998a). No changes in the heart or blood vessels were observed in rats following oral exposure to doses as high as 9,393 mg U/kg/day as uranyl nitrate hexahydrate, 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as uranium peroxide, 10,611 mg U/kg/day as uranium tetrafluoride, 10,819 mg U/kg/day as uranyl fluoride,

12,342 mg U/kg/day as uranium dioxide, 11,650 mg U/kg/day as uranium trioxide, or 7,859 mg U/kg/day as uranyl acetate dihydrate (Maynard and Hodge 1949). Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and sacrificed. No uranium-related histopathological changes were found in the heart, and no changes in heart weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg/kg/day; females: up to 43.02 mg/kg/day) for 91 days. No treatment-related cardiac histopathological changes were noted, and no changes in heart weights were detected (Gilman et al. 1998b). Male New Zealand rabbits also were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, with no histopathological or organ weight changes (Gilman et al. 1998c).

Gastrointestinal Effects. A volunteer given a single dose of 1 g uranyl nitrate (14.3 mg/kg) and observed for clinical signs and symptoms within 24 hours after intake suffered acute nausea, vomiting, and diarrhea within a few hours of administration. All clinical signs returned to normal within 24 hours after administration of the oral uranyl nitrate dose (Butterworth 1955). Paralytic ileus was reported in a male after the deliberate ingestion of 15 g uranyl acetate (Pavlakis et al. 1996). While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. No other reports of gastrointestinal effects after acute-duration exposure to uranium in either humans or laboratory animals were available.

Studies of intermediate-duration exposure to uranium compounds were available for laboratory animals. In one study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and sacrificed. No treatment-related histopathological changes were found, and no changes in organ weights were noted (Gilman et al. 1998a). In a study of longer duration, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and then sacrificed. No treatment-related histopathological changes were found in the gastrointestinal tract, and no changes in stomach and intestinal weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg/kg/day; females: 0 up to 43.02 mg/kg/day) for 91 days. No treatment-related histopathological changes were found, and no changes in organ weights (i.e., colon, duodenum, stomach [gastric cardia, fundus, and pylorus]) were noted (Gilman et al. 1998b). Male New Zealand

rabbits were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days, with no histopathological or organ weight changes found (Gilman et al. 1998c).

Hematological Effects. In one case report, a male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was unremarkable; however, an anemia developed and continued to progress over the next 8 weeks, along with persistent renal dysfunction (Pavlakis et al. 1996). While the authors attributed the renal dysfunction to uranium ingestion, the etiology of the anemia was unknown. The patient also suffered from peptic ulcer disease which may have been related to the anemia.

The majority of animal studies show no effect of uranium on hematological parameters after oral exposure. Exposure to uranium as uranyl nitrate in drinking water had no hematological effects in Sprague-Dawley rats after 28 days (up to 40 mg U/kg/day) or 91 days (up to 53 mg U/kg/day) (Gilman et al. 1998a), or in New Zealand rabbits after 91 days (up to 43 mg U/kg/day) (Gilman et al. 1998b, 1998c). Exposure to a variety of uranium compounds in feed had no effect on hematological parameters in intermediate- and chronic-duration studies (Maynard and Hodge 1949). One study reported a significant increase in the hematocrit and hemoglobin values, the mean corpuscular hemoglobin concentration, and the number of erythrocytes at 9 mg U/kg/day as uranyl acetate in drinking water for 4 weeks, but not at 4.5 mg U/kg/day and lower doses (Ortega et al. 1989a).

In a chronic-exposure feeding study, mild anemia and an increased leucocyte count were observed in rats given uranyl nitrate hexahydrate doses corresponding to 33 mg U/kg/day for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

Musculoskeletal Effects. In one human case report, a human male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. The patient suffered from increasing rhabdomyolysis (biochemically characterized by increased creatine kinase). At 6 months following the

initial toxic insult, the rhabdomyolysis had resolved, and the subject showed no residual signs of muscle toxicity (Pavlakis et al. 1996). The etiology of this effect is unknown.

In the available animal studies, the existing data provide evidence that uranium exposure does not cause detectable damage to the musculoskeletal system. Histopathological examination of muscle after exposure to uranium in drinking water as uranyl nitrate showed no effects in Sprague-Dawley rats after 28 days (up to 40 mg U/kg/day) or 91 days (up to 53 mg U/kg/day) (Gilman et al. 1998a), or in New Zealand rabbits after 91 days (up to 43 mg U/kg/day) (Gilman et al. 1998b, 1998c).

Hepatic Effects. Few human data are available on the hepatic effects of uranium. In one case report, a human male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in a failed suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. The patient suffered from increasing liver dysfunction, characterized by increased serum levels of ALT, AST, and GGK. Six months following the initial toxic insult, the patient had no residual signs of hepatic toxicity (Pavlakis et al. 1996). The etiology of this effect is unknown, although histological signs of hepatic toxicity have been observed in animals after oral exposure to uranium.

In the available animal studies, the existing data provide evidence that uranium exposure can damage the liver, although the etiology for this effect is not certain. In an acute-duration study in which Sprague-Dawley rats were given single gavage doses of 5.6 or 118 U/kg as uranyl acetate dihydrate, microhemorrhagic foci in the liver were observed at both doses tested (Domingo et al. 1987).

Ingested uranium doses were also hepatotoxic to dogs in studies of intermediate-duration exposure. When uranyl fluoride was tested at 7.7, 15.4, 77.3, 386.7, or 3,864 mg U/kg/day for 30 days, fatty infiltration was seen in dogs at the 15.4 mg U/kg/day dose level (Maynard and Hodge 1949). In other tests, uranium tetrachloride induced minimal hepatic lesions at a dose level of 313 mg U/kg/day; uranium peroxide induced mild degeneration at a dose level of 386 mg U/kg/day; uranium dioxide induced mild degeneration at a dose level of 441 mg U/kg/day; uranium trioxide induced slight fatty infiltration at a dose level of 416 mg U/kg/day; triuranium octaoxide induced mild fatty changes at a dose level of 5,653 mg U/kg/day; sodium diuranate induced mild degeneration at a dose level of 37.5 mg U/kg/day;

uranium tetrafluoride caused degenerative fatty changes at a dose level of 15,159 mg U/kg/day; and uranyl nitrate hexahydrate induced minimal hepatic degeneration at a dose level of 237 mg U/kg/day (Maynard and Hodge 1949).

Hepatic toxicity was also found several other studies. In one study, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg/kg/day; females: up to 53.56 mg/kg/day) for 91 days and then sacrificed. Hepatic lesions, which included anisokaryosis, vesiculation, increased portal density, perivenous vacuolation, and homogeneity, were observed in the liver at all doses (Gilman et al. 1998a), although the dose ranging portion of this study found no effects at essentially the same doses as those discussed below (Gilman et al. 1998c). However, in New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: 0, 0.05, 0.20, 0.88, 4.82, and 28.70 mg/kg/day; females: 0, 0.49, 1.32, and 43.02 mg/kg/day) for 91 days, no treatment-related histopathological changes were found, and no changes in liver weights were noted (Gilman et al. 1998b). In contrast, another study by the same investigator in male New Zealand rabbits exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg/kg/day) for 91 days found irregular accentuation of zonation in the liver, accompanied by increased variation in hepatocellular nuclear size, nuclear pyknosis, and extensive cytoplasmic vacuolization. These changes were found to be treatment-related but not dose-related (Gilman et al. 1998c).

In other intermediate-duration studies, no effects were seen on the liver of dogs given oral doses of 9,393 mg U/kg/day as uranyl nitrate hexahydrate or 191 mg U/kg/day as ammonium diuranate for 30 days (Maynard and Hodge 1949). Similarly, no effects were seen on the liver of rats given oral doses of 8,769 mg U/kg/day as uranium tetrachloride, 11,033 mg U/kg/day as triuranium peroxide, 10,818 mg U/kg/day as uranyl fluoride, 12,342 mg U/kg/day as uranium dioxide, 11,650 mg U/kg/day as triuranium trioxide, or 7,859 mg U/kg/day as uranium acetate dihydrate for 30 days (Maynard and Hodge 1949). Sprague-Dawley rats (10/sex/dose, 60 g) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg/kg/day; females: up to 40.0 mg/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in liver weights were noted (Gilman et al. 1998a).

Renal Effects. Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the renal proximal tubules of humans and animals. In this regard, uranium is a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury) (Goodman 1985).

Few human data are available that adequately describe the dose-response toxicity of uranium after an oral exposure. In one human case report study, a male (no age or weight given), was admitted to hospital following the deliberate ingestion of 15 g of uranyl acetate, along with an unknown quantity of benzodiazepine, in failed a suicide attempt. While body weight was not reported, the dose would be approximately 131 mg U/kg for a 70 kg reference man. Initial blood chemistry was normal; however, 16 hours after admission, his blood urea levels had doubled and creatinine levels had increased 3.5-fold, which suggested renal damage. A diagnosis of acute nephrotoxicity from heavy metal exposure was made, and chelation therapy with Ca-EDTA, sodium bicarbonate, and mannitol was initiated. His plasma uranium on the day following commencement of chelation therapy was 3.24 μmol/L, decreasing to 1.18 μmol/L after 5 days of chelation and dialysis. Chelation therapy was then stopped; however, dialysis continued for 2 weeks at which point kidney function recovered sufficiently to allow withdrawal of dialysis therapy. The patient's anemia persisted over the next 8 weeks, along with persistent renal dysfunction. Additional chelation therapy was initiated with both Ca EDTA and Ca DTPA (diethylenetriamine pentaacetic acid) without success. At 6 months following the initial toxic insult, the patient still suffered from an incomplete Fanconi syndrome (renal tubular acidosis) requiring supplemental sodium bicarbonate therapy on a daily basis (Pavlakis et al. 1996). The authors suggested that pre-existing peptic ulcer disease in this patient may have exacerbated toxicity by increased absorption of uranium through the damaged stomach mucosal layer.

Although there is little additional information about renal effects in humans following oral exposure to uranium compounds, there is sufficient information in animals with high exposures to both soluble and insoluble uranium to permit the conclusion that uranium has a low order of metallotoxicity in mammals. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce severe, perhaps fatal, injury at the levels of exposure reported for uranium in the literature. The negative findings regarding renal injury among workers exposed over long time periods to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurs in survivors upon discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949c; Spiegl 1949; Stokinger et al. 1953).

Male Sprague-Dawley rats exposed to a single gavage dose of 5.6 mg U/kg suffered slight renal dysfunction and minimal microscopic lesions in the tubular epithelium (Domingo et al. 1987).

An intermediate-duration oral study in which dogs were given doses of 37.5 or 187 mg U/kg/day as sodium diuranate in the diet for 30 days found elevated peak NPN and BUN but not in a dose-dependent manner. Blood sugar was also slightly elevated. Necropsy findings revealed mild degeneration and necrosis in the kidneys at the higher dose level but only minimal degeneration and necrosis at 37.5 mg U/kg/day (Maynard and Hodge 1949). In other animal studies, exposure to uranium (uranyl fluoride, triuranium octaoxide, uranyl nitrate hexahydrate, uranium tetrachloride, uranium peroxide, ammonium diuranate) at oral doses as low as 0.05 mg U/kg/day and as high as 7,859 mg U/kg/day for 30 days were damaging to the kidneys. Nephrotoxic effects found in these animals ranged from minimal microscopic lesions in the tubular epithelium (for low doses) to extensive necrosis in the tubular epithelium (for high doses of soluble compounds) (Maynard and Hodge 1949). No effects on the kidneys were found in rats similarly exposed to 12,342 mg U/kg/day as uranium dioxide or 11,650 mg U/kg/day as uranium trioxide for 30 days (Maynard and Hodge 1949); perhaps, this finding was due to the low gastrointestinal absorption of the insoluble salt.

In intermediate-duration studies, dogs orally exposed to up to 95 mg U/kg/day as uranyl nitrate hexahydrate for 138 days suffered elevated NPN, BUN, glucosuria, and proteinuria at doses of 95 mg U/kg/day and higher, no effect was seen at 47 mg U/kg/day (Maynard and Hodge 1949). Exposure of mice to 452 mg U/kg/day as uranyl fluoride for 48 weeks resulted in the kidneys being tan-gray in color with nodules on the surface (Tannenbaum and Silverstone 1951). However, the kidneys appeared to be normal upon microscopic examination. In other studies, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: 0.05, 0.27, 1.34, 6.65, 35.3 mg U/kg/day; females: 0.07, 0.33, 1.65, 7.82, 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found, and no changes in organ weights were noted. The only effect observed was a significant increase in serum uric acid in females at 40 mg U/kg/day (1.64 vs. 1.18 mg/dL in controls). This 28-day dose range finding study found few adverse effects at even the highest dose, but was followed by a 91-day study of the same regimen, with significantly different results. In that study, Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in drinking water (males: <0.0001, 0.06, 0.31, 1.52, 7.54, 36.73 mg U/kg/day; females: <0.0001, 0.09, 0.42, 2.01, 9.98, 53.56 mg U/kg/day) for 91 days were found to have renal lesions of the tubules (apical nuclear displacement and vesiculation, cytoplasmic vacuolation, and dilation), glomeruli (capsular sclerosis), and interstitium (reticulin sclerosis and lymphoid cuffing) observed in the lowest exposure groups. No explanation for the differences was provided (Gilman et al. 1998a).

Two studies by MacDonald-Taylor et al. (1992, 1997) produced similar renal lesions in rabbits. In these studies, weanling New Zealand male rabbits were exposed to uranium for 91 days via drinking water containing 0, 24, or 600 mg/L uranyl nitrate Doses were not calculated from water intake. Calculations using default reference values for this species result in doses of 0, 0.93, and 23 mg U/kg/day (EPA 1998). Each treatment group was divided into 3 subgroups: immediate sacrifice and either 45-day or 91-day recovery period. At the end of the recovery periods, rabbits were sacrificed and renal sections prepared for electron microscopy. Thickness of the glomerular basement membrane (GBM) was measured from electron micrographs. Measurements were taken at approximately 35 µm increments; 600–900 measurements were made for each treatment group and recovery period. Uranyl nitrate exposure resulted in thickening of the membrane in the rabbits. Control thickness was approximately 80 µm; the thickness was 96.3 µm immediately after exposure at the low dose and increased to 103 µm after a 91-day recovery. Initial thickness after 91 days exposure in the high-dose group was 109 µm and had increased to 117 µm after a 91-day recovery period. Similarly, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days (Gilman et al. 1998b). Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in male rabbits. In the males, a significant increased incidence of anisokaryosis and nuclear vesiculation was observed in all treated groups. Nuclear pyknosis and hyperchromicity were observed in all treated groups except in the 0.05 mg U/kg/day treatment group. Tubular dilation, atrophy, protein casts, and collagen sclerosis were observed at 4.82 and 28.70 mg U/kg/day. Reticulin sclerosis was observed at 0.88, 4.82, and 28.70 mg U/kg/day. Anisokaryosis and nuclear vesiculation were observed in all treated female groups. Tubular dilation and atrophy were also observed. Collagen sclerosis was observed at 43.02 mg U/kg/day, reticulin sclerosis was observed at 0.49 and 43.02 mg U/kg/day. Females drank 65% more water than the males; however, the females appeared to be less affected by the exposure regimen. These exposed females did develop significant tubular nuclear pathology in the lowest exposure group, but not to the degree of the exposed males (Gilman et al. 1998b). The LOAEL of 0.5 mg U/kg/day from this study was used to develop an intermediate-duration MRL of $2.0x10^{-3}$ mg/kg/day for oral exposure to uranium and is shown in Table 2-3 and plotted in Figure 2-3.

In another study, male New Zealand rabbits were exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg U/kg/day) for 91 days, and were then allowed to recover for several weeks after dosing ceased (Gilman et al. 1998c). No differences in urinary parameters were noted in any of the groups exposed to the 1.36 mg U/kg/day dose. Kidney weight as a percentage of body weight was

significantly increased in the 40.98 mg U/kg/day group (compared to controls) immediately after exposure, but was not significantly increased after 45 days of exposure. In rabbits exposed to the 40.98 mg U/kg/day dose, urinary output was decreased at week 1, with increased excretion of glucose, protein and leucine aminopeptidase activity. Similar results were observed at week 4 after dosing began. Seven days after the start of the recovery period, urinary volume was increased and glucose secretion remained elevated. Protein and leucine aminopeptidase activity excretion returned to normal. At 3, 5, and 13 weeks post-exposure, urinary parameters were normal. Groups exposed to 40.98 mg U/kg/day had increases in percentage and total lymphocyte counts after the 91-day recovery period but not at the end of exposure. Focal dilation of renal proximal tubules was observed in both treated groups accompanied by cytoplasmic vacuolation. Nuclear changes included apical displacement and irregular placement with vesiculation, anisokaryosis, and pyknosis. Tubular basement membranes were normal early in injury but thickened focally during recovery. Changes induced by exposure at 40.98 mg U/kg/day persisted for up to 45 days and in some cases for 91 days (Gilman et al. 1998c).

Endocrine Effects. No endocrine effects after oral intake of uranium have been reported in humans. Few endocrine effects have been reported after uranium exposure in laboratory animals. In animal studies, a dose of 0.07 mg U/kg/day as uranyl nitrate hexahydrate for 16 weeks in drinking water resulted in degenerative changes in the thyroid epithelium and altered thyroid function in Wistar rats (Malenchenko et al. 1978). Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related histopathological changes were found in any of the endocrine organs studied (adrenal, pancreas, parathyroid, pituitary, thymus, thyroid), and no treatment-related changes in these organ weights were noted (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days. No treatment-related histopathological changes were found, and no weight changes in the adrenal, pancreas, parathyroid and pituitary glands were noted (Gilman et al. 1998b). Male New Zealand rabbits exposed to uranium as uranyl nitrate in drinking water (1.36 and 40.98 mg U/kg/day) for 91 days also failed to show any treatment-related histopathological or organ weight changes (Gilman et al. 1998c). In another study, Sprague-Dawley rats (15/sex/dose) were exposed to uranium as uranyl nitrate in the drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days. Thyroid lesions were observed in both sexes (multifocal reduction of follicular

size, increased epithelial height in males at 0.31 mg U/kg/day and females at 2.01 mg U/kg/day). A decreased amount and density of colloid in the thyroid was observed in males only.

Body Weight Effects. No body weight effects after oral intake of uranium have been reported in humans.

Oral exposure to uranium compounds has caused body weight effects in animals, but these effects are not necessarily the result of systemic toxicity. The initial loss of body weight observed in animals exposed to high doses of uranium in the diet in acute-, intermediate-, and chronic-duration studies is usually accompanied by decreased food consumption in these animals. The decreased food consumption could be due to the aversive taste of uranium compounds in food. Subsequent acclimatization of the animals to the taste would normalize food intake and, consequently, reverse the initial loss of body weight. Thus, the changes in body weight seen in such studies may be due more to reduction in food consumption due to distaste than to uranium-specific chemical or radiological toxicity. More recent studies in which sugar was added to the drinking water of animals to remove the aversive effect of uranium (Ortega et al. 1989a) support this hypothesis.

Rats given single oral doses of 664 mg U/kg as uranyl nitrate hexahydrate or 55 mg U/kg as uranium peroxide (Maynard et al. 1953), 7,859 mg U/kg as uranium acetate dihydrate for 30 days (Maynard and Hodge 1949), or 664 mg U/kg as uranyl nitrate hexahydrate for 30 days in the feed suffered unspecified decreases in body weight gain (Maynard et al. 1953). Similarly, body weight losses of 18, 35, 27, 20, and 29%, respectively, were observed in rats given oral doses of 886 mg U/kg/day as uranium tetrachloride, 1,081 mg U/kg/day as uranyl fluoride, or 664 mg U/kg/day as uranyl nitrate hexahydrate for 30 days (Maynard and Hodge 1949); rabbits given oral doses of 14.2 mg U/kg/day as uranyl nitrate hexahydrate for 30 days (Maynard and Hodge 1949); and rats given oral doses of 270 mg U/kg/day as uranyl fluoride for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

No harmful effects on body weight were seen in rats given 12,342 mg U/kg as uranium dioxide or 11,650 mg U/kg as uranium trioxide for 30 days (Maynard and Hodge 1949), mice given 1,100 mg U/kg as uranyl nitrate hexahydrate for 18 weeks or 462 mg U/kg as uranyl nitrate hexahydrate for 48 weeks (Tannenbaum and Silverstone 1951), or in Sprague-Dawley rats exposed to uranium as uranyl nitrate in drinking water at doses up to 35.3 mg U/kg/day (males) and 40 mg U/kg/day (females) for 28 days or up

to 36.73 mg U/kg/day (males) and 53.56 mg U/kg/day (females) for 91 days (Gilman et al. 1998a). No alterations in body weights were observed in rats given 12,341 mg U/kg as uranium dioxide or 10,611 mg U/kg as uranium hexafluoride for 2 years, or dogs given 8 mg U/kg as uranyl fluoride or 95 mg U/kg as uranyl nitrate hexahydrate for 1 year (Maynard and Hodge 1949; Maynard et al. 1953). In animal studies, reduced food intake was observed following a single oral dose of 5.6 mg U/kg as uranyl nitrate hexahydrate to rats (Domingo et al. 1987) and in a 48-week study in rats and mice at 1,100 mg U/kg/day as uranyl nitrate hexahydrate (Tannenbaum and Silverstone 1951). It has been suggested that this reduced food intake is a result of loss of appetite due to the unpalatability of the uranium compounds in the animals' food (Dygert 1949e).

2.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding the effects of uranium on the immune system in humans following oral exposure for any duration.

In laboratory animals, oral exposure of rats, mice, and rabbits to uranium had no significant effect on immune system function. In one study Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related effects were noted in the immunological/lymphoreticular tissues examined (bone marrow, mesenteric and mediastinal lymph nodes, spleen, and thymus) (Gilman et al. 1998a). In addition, New Zealand rabbits were exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days. No histopathological changes were found, and no changes in the bone marrow, mesenteric and mediastinal lymph nodes, or thymus were noted (Gilman et al. 1998b). Rats exposed to oral doses of 0.07 mg U/kg as uranyl nitrate hexahydrate for 4 weeks showed an increase in spleen weight but the body weights of both the control and test animals were not provided, making it impossible to determine whether the net change in spleen weight had any toxicological significance (Malenchenko et al. 1978). Sprague-Dawley rats exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days showed sinus hyperplasia of the spleen in both sexes at the highest dose (males: 36.73; females: 53.56 mg U/kg/day). No lesions were observed in bone marrow, mesenteric and medistinal lymph nodes, or in the thymus (Gilman et al. 1998a). In other studies with mice and rats, no histological changes in the spleen, lymph nodes, or bone marrow were seen

in the animals following administration of up to 5,000 mg U/kg of various uranium compounds (uranyl nitrate hexahydrate, uranyl fluoride, uranium dioxide, uranium peroxide, uranium tetrafluoride, uranium tetrachloride, triuranium octaoxide, or uranium trioxide) in the diet for 48 weeks or 2 years. No consistent hematological changes were found in hematocrit, hemoglobin, or white blood cell counts (Maynard et al. 1953; Tannenbaum and Silverstone 1951). No other specific immunological tests were performed.

2.2.2.4 Neurological Effects

No studies were located for humans regarding neurological effects following oral exposure to uranium compounds.

No evidence of histological effects in nervous tissue have been reported after oral exposure to uranium compounds in animal studies, although one study reported clinical signs of neurotoxicity. Piloerection, tremors, hypothermia, pupillary size decreases and exophthalmos were seen at all dose levels in a study with Sprague-Dawley rats given single gavage doses of 11, 22, 45, 90, 179, 358, or 717 mg U/kg as uranyl acetate dihydrate. The signs became more severe as the number of days post-treatment increased (Domingo et al. 1987). In another study, Sprague-Dawley rats (10/sex/dose) were exposed to uranium as uranyl nitrate in drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days and then sacrificed. No treatment-related effects were noted in the three sections of brain examined histopathologically (Gilman et al. 1998a). No treatment-related effects on the brains of Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in the drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days were found (Gilman et al. 1998a). Additionally, New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days showed no brain histopathological changes.

The LOAEL value for this study is presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.5 Reproductive Effects

No human studies were located regarding reproductive effects following oral exposure to uranium compounds. Limited animal studies have shown some effects on reproductive function but generally no evidence of histopathological damage to reproductive tissues. No reproductive effects or changes in

reproductive organ weights were found in the epididymis, testes, ovary, or uterus of Sprague-Dawley rats (10/sex/dose) exposed to uranium as uranyl nitrate in the drinking water (males: up to 35.3 mg U/kg/day; females: up to 40.0 mg U/kg/day) for 28 days (Gilman et al. 1998a). No reproductive effects or changes in reproductive organ weights were found in the epididymis, testes, ovary, or uterus of Sprague-Dawley rats (15/sex/dose) exposed to uranium as uranyl nitrate in drinking water (males: up to 36.73 mg U/kg/day; females: up to 53.56 mg U/kg/day) for 91 days (Gilman et al. 1998a). New Zealand rabbits exposed to uranium as uranyl nitrate in the drinking water (males: up to 28.70 mg U/kg/day; females: up to 43.02 mg U/kg/day) for 91 days showed no histopathological or organ weight changes in the epididymis, ovary, testes, or uterus (Gilman et al. 1998b). No effects on fertility were found in mice given oral gavage doses of 14 mg U/kg/day as uranyl acetate dihydrate in a 4- to 8-week study (Paternain et al. 1989). In a 64-day study with Swiss-Webster mice, no significant differences in the total implantations, early and late resorptions, or the number of live and dead fetuses were observed in females mated with male mice treated with drinking water doses of 45 mg U/kg/day as uranyl acetate dihydrate, as compared to untreated controls; but a reduced sperm count was observed in the 11.2 mg U/kg/day group (Llobet et al. 1991). However, in another study, offspring of male Swiss mice exposed to 2.8, 5.6, or 14 mg U/kg/day intragastrically as uranyl acetate dihydrate for 38–60 days before mating with female mice that had received the same doses orally for 14 days prior to mating exhibited reproductive abnormalities manifested as reduced implantations and increased fetal resorptions. The average number of total implantations was only different in the 2.8 mg U/kg/day group (Paternain et al. 1989). Maternal toxicity (reduced weight gain and food consumption, increased relative liver weight) was seen at all doses in 20 pregnant Swiss mice given uranyl acetate dihydrate (3, 6, 14, or 28 mg U/kg/day) by gavage on gestation days (Gds) 6–15 and sacrificed on Gd 18 to assess potential maternal and fetal toxicity (Domingo et al. 1989a).

In chronic-duration studies, male rats given high oral doses (331 mg U/kg/day) of uranyl nitrate hexahydrate in the diet for 2 years developed testicular degeneration; female rats given oral doses of 664 mg U/kg/day as uranyl nitrate hexahydrate for 2 years had reduced litter sizes (Maynard et al. 1953). Since incidence and dose-response data were not provided in this report, its significance is unclear.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for reproductive effects from exposure to uranium by the oral route are presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.6 Developmental Effects

No studies were located that reported developmental effects in humans following oral exposure to uranium for any duration. Animal studies indicate that oral exposure to uranium can cause developmental effects, but only at relatively high doses.

In animal studies, pregnant Swiss mice were exposed to uranium as uranyl acetate dihydrate by gavage in water at a dose of 0.028, 0.28, 2.8, 28 mg U/kg/day from day 13 of gestation through postnatal day 21. Treatment had no significant effects on mean litter size at birth or on day 4, but litter size was significantly decreased at postnatal day 21 at 28 mg U/kg/day (5.5 vs. 8.8 in water-only controls). The viability index (number of pups viable at day 21/number of pups born) and the lactation index (number of pups viable at day 21/number of pups retained at day 4) were significantly decreased in the 28 mg U/kg/day group. No significant differences were observed in developmental signs (pinnae unfolding, lower incisor eruption, eye opening), or in pup weight or body length (Domingo et al. 1989b). Structural variations were not assessed in this report.

The offspring of male Swiss mice exposed to 2.8, 5.6, and 14 mg U/kg/day intragastrically as uranyl acetate dihydrate for 38–60 days before mating with female mice that had received the same doses orally for 14 days prior to mating exhibited developmental defects. The average number of total implantations was only different in the 2.8 mg U/kg/day group. The numbers of late resorptions and dead fetuses were significantly increased for the 14 mg U/kg/day group. Significantly reduced viability was observed in the 5.6 mg U/kg/day group. A dose-response relationship was observed for reduced offspring growth as determined by body weight and body length (Paternain et al. 1989). Similarly, a dose-related fetotoxicity, manifested as reduced fetal body weight and length, an increase in the incidence of stunted fetuses and external and skeletal malformations, and developmental variations, was reported in the offspring of 20 pregnant Swiss mice given uranyl acetate dihydrate (3, 6, 14, and 28 mg U/kg/day) by gavage on Gds 6–15 and sacrificed on Gd 18. External malformations included a significant increase in the incidence of cleft palate ($6 mg U/kg/day) and hematomas (at 3 and 28 mg U/kg/day). Underdeveloped renal papillae were seen in the 3 and 14 mg U/kg/day groups. An increase in the incidence of skeletal abnormalities (bipartite sternebrae and reduced or delayed ossification of the hind limb, fore limb, skull, and tail) were seen in the 14 and 28 mg U/kg/day groups. Embryolethality was not found at any of the dose levels tested (Domingo et al. 1989a); however, in another study, embryolethality was found in

offspring of mice given an oral gavage dose of 14 mg U/kg/day as uranyl acetate dihydrate in a 4–8-week study (Paternain et al. 1989).

In another study, the mean litter size of the offspring of female Sprague-Dawley rats was significantly lower ($p<0.05$) at an oral exposure of 28 mg U/kg/day uranyl acetate dihydrate on postnatal day 21 when a group of rats were exposed to 0.028, 0.38, 2.8, or 28 mg U/kg/day for 30 days. The viability index (day 21:day 0) and lactation index were also significantly reduced at this exposure level. No differences in the developmental milestones monitored (pinna attachment, eye opening, incisor eruption) were observed in the treated animals. Treatment with uranium had no significant effect on length of gestation and sex ratios and on mean litter size at birth or postnatal day 4 as well as on body weight or pup body length throughout lactation. There was no significant effect on food consumption during the periods of late gestation and lactation (Domingo et al. 1989b).

The highest NOAEL values and all reliable LOAEL values in each species and duration category for developmental effects from exposure to uranium by the oral route are presented in Table 2-3 and plotted in Figure 2-3.

2.2.2.7 Genotoxic Effects

No information was located regarding the toxic action of uranium on genetic material in humans or animals following oral exposure for any duration.

Because uranium is a predominantly alpha-emitting radionuclide, current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a potential for genotoxicity from uranium's radioactivity (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) (see Appendix D for a review of the hazards associated with radionuclide exposure). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No evidence linking oral exposure to uranium to human cancer has been found. Although natural, depleted, or enriched uranium and uranium compounds have not been evaluated in rodent cancer bioassays by any route by the NTP (BEIR 1980, 1988, 1990; Hahn 1989; Sanders 1986; UNSCEAR 1982, 1986, 1988), there is potential for the carcinogenicity of uranium, since it emits primarily alpha radiation. Nevertheless, no evidence has been found to associate human exposure to uranium compounds and carcinogenesis. The National Academy of Sciences has determined that bone sarcoma is the most likely cancer from oral exposure to uranium; however, their report noted that this cancer has not been observed in exposed humans and concluded that exposure to natural uranium may have no measurable effect (BEIR IV).

Similarly, the results of several oral studies with uranium in several species were negative for evidence of cancer induction (Maynard and Hodge 1949; Maynard et al. 1953; Tannenbaum and Silverstone 1951).

No studies were located that provided evidence that oral exposure of humans to uranium as an alpha-emitting radiation source causes cancer. The available human data on the relative potential of ingested radium and uranium isotopes to induce cancers in humans concluded that the cumulative lifetime risk to 1 million people, each ingesting 5 pCi of a radium isotope (^{226}Ra, ^{228}Ra, and ^{224}Ra) per day, for the induction of skeletal cancers (bone sarcomas and carcinomas of the head sinuses) is 9 bone sarcomas and 12 head carcinomas for ^{226}Ra, 22 bone sarcomas for ^{228}Ra, and 1.6 bone sarcomas for ^{224}Ra. Assuming that the risk per rad of the average skeletal dose is equal for ^{226}Ra and uranium isotopes with half-lives exceeding 1,000 years, and that the equilibrium skeletal content is 25 times the daily ingestion of ^{226}Ra but 11 times the daily ingestion of long-lived uranium, the cumulative lifespan risk to 1 million people, each ingesting 5 pCi per day of ^{234}U (0.0008 µg), ^{235}U (2.3 µg), or ^{238}U (15 µg), is estimated to be about 1.5 bone sarcomas. However, no cancers would be expected if the incidence is found to vary with the square of the dose instead of linearly (Mays et al. 1985). The BEIR IV report came to the same conclusion, but reserved the opinion that bone sarcomas might be caused by highly enriched uranium. The report estimated a lifetime risk of excess bone sarcomas per million people of 1.5 if soluble uranium isotopes were ingested at a constant daily rate of 1 pCi/day (0.037 Bq/day). The number of bone sarcomas that occur naturally in a population of a million people is 750. However, no quantitative risk coefficient estimates for developing human exposure protection benchmarks were provided in this report. In addition, the BEIR IV analysis was presumably based on generic short-lived alpha-emitting sources,

such as radon that have a higher potential for inducing cancer, and not on radionuclides with relatively longer radioactive half-lives like ^{238}U, ^{235}U, and ^{234}U. Perhaps more importantly, the BEIR IV report concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect" (BEIR IV 1988).

The available long-term feeding studies in rats, mice, dogs, and rabbits found no evidence of cancer induction upon histopathological examination of selected organs and tissues. The available studies tested mice, dogs, and rabbits with extreme intakes of uranium corresponding to radioactivity exposures of as high as $1.0x10^4$ nCi/kg/day ($3.7x10^5$ Bq/kg/day) ($1.5x10^4$ mg U/kg/day) for 30 days (Maynard and Hodge 1949; Tannenbaum and Silverstone 1951) or rats and dogs at $8.2x10^3$ nCi/kg/day ($3x10^5$ Bq/kg/day) ($1.2x10^4$ mg U/kg/day) for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

2.2.3 Dermal Exposure

2.2.3.1 Death

No deaths have been reported in humans as a result of dermal exposure to uranium.

Deaths have occurred in animals after dermal exposure to uranium compounds from both single and repeated exposures. Generally, the more water-soluble uranium compounds were the most toxic and the rabbit was the most sensitive species. Deaths were due to renal failure.

In a series of 4-hour exposures to uranium compounds followed by washing with detergent and a 30-day observation period, the lowest reported LD_{50} value was 28 mg U/kg as uranyl nitrate in an ethereal solution in New Zealand rabbits (Orcutt 1949). Calculated LD_{50} values for identical exposures to uranyl nitrate were 1,190 mg U/kg for guinea pigs and 4,286 mg U/kg for mice. Insufficient fatalities occurred to calculate an LD_{50} for rats, but the mortality curve fell between that of the rabbits and the guinea pigs. Deaths mainly occurred 5 to 7 days after exposure and were due to renal failure. Similar experiments with other uranium compounds in rabbits using a lanolin vehicle showed that water-soluble compounds (uranyl fluoride, uranium tetrachloride, uranium pentachloride) were the most toxic; the slightly soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) had intermediate toxicity; and the

water insoluble compounds (uranium tetrafluoride, uranium dioxide, uranium peroxide, triuranium octoxide) caused no deaths (Orcutt 1949).

Chemically induced renal failure caused 100% mortality in male Wistar rats after 5 daily exposures to 237 or 1,928 mg U/kg/day as uranyl nitrate hexahydrate or ammonium uranyl tricarbonate, respectively, applied in a water-Vaseline® emulsion (De Rey et al. 1983). A 60% mortality rate was also reported for other male Wistar rats that received daily applications of 1,965 mg U/kg as uranyl acetate dihydrate for 1–11 days. No deaths were reported for other Wistar rats similarly treated with 2,103 mg U/kg/day as ammonium diuranate or to an unspecified dose of uranium dioxide (De Rey et al. 1983).

Intermediate-duration dermal exposure in guinea pigs indicated that smaller repeated doses were better tolerated than a large single dose when the total exposure was the same. In a 4-week experiment where exposure was to 379 mg U/kg as uranyl nitrate for 3 days per week, 14% mortality was observed (Orcutt 1949). If the same cumulative dose (4,741 mg U/kg) had been given in a single application, 86% mortality would have been expected.

The LD_{50} values for each species and other LOAEL values for mortality from exposure to uranium through the dermal route are presented in Table 2-4.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans following dermal exposure to uranium compounds for acute, intermediate, or chronic durations.

No studies were located regarding the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or endocrine effects of uranium in animals following acute-, intermediate-, or chronic-duration exposure; regarding the renal effects following intermediate- or chronic-duration exposure; regarding the dermal or body weight effects following chronic-duration exposure; or regarding ocular effects following acute- or chronic-duration exposure. The existing animal data on renal, dermal, and body weight effects are limited to acute- and intermediate-duration exposures.

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Rat (Wistar)	1-11 d 1x/d				237 M (100% mortality in 5 days)	De Rey et al. 1983 UO2(NO3)2*6H2O
Rat (Wistar)	1-11 d 1x/d				1965 M (60% mortality in 11 days)	De Rey et al. 1983 UO2(C2H3O2)2*2H2O
Rat (Wistar)	1-11 d 1x/d				1928 M (100% mortality in 5 days)	De Rey et al. 1983 (NH4)8U2O4(CO3)3
Rat (Wistar)	4 hr (EPICU)				101 F (LD_{50})	Orcutt 1949 UO2(NO3)2*6H2O
Mouse (albino)	4 hr (EPICU)				4286 F (LD_{50})	Orcutt 1949 UO2(NO3)2*6H2O
Gn pig	4 hr (EPICU)				2520 (LD_{50})	Orcutt 1949 UCl4
Gn pig (NS)	once (EPICU)				1190 (LD_{50})	Orcutt 1949 UO2(NO3)2*6H2O

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL			Reference Chemical Form
				Less Serious (mg/kg)	Serious (mg/kg)		
Rabbit (New Zealand)	4 hr (EPICU)				344	(67% mortality)	Orcutt 1949 UCl5
Rabbit (New Zealand)	4 hr (EPICU)				188	(50% mortality)	Orcutt 1949 UCl4
Rabbit (New Zealand)	4 hr (EPICU)				666	(67% mortality)	Orcutt 1949 UO3
Rabbit (New Zealand)	once 4 hr (EPICU)				198	(33% mortality)	Orcutt 1949 (NH4)2U2O7
Rabbit (New Zealand)	4 hr (EPICU)				28	(LD_{50})	Orcutt 1949 UO2(NO3)2*6H2O
Rabbit (New Zealand white, New Zealand red, checker, chinchilla, or mixed)	4hr (EPICU)				3091	(83% mortality)	Orcutt 1949 UO2F2

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
Systemic						
Rat (Wistar)	1-11 d 1x/d	Renal			1965 M (renal failure)	De Rey et al. 1983 UO2(C2H3O2)2*2H2O
		Bd Wt			1965 M (70% weight loss)	
		Dermal	3929 M			
Rat (Wistar)	1-11 d 1x/d	Dermal	1928 M			De Rey et al. 1983 (NH4)8U2O4(CO3)3
		Bd Wt		1928 M (slight initial weight loss)		
Rat (Wistar)	1-11 d 1x/d	Renal			2670 M (renal failure)	De Rey et al. 1983 (NH4)2U2O7
		Dermal		2670 M (mild lesions)		
		Bd Wt			2670 M (severe weight loss)	
Rat (Wistar)	1-11 d 1x/d	Renal			237 M (renal failure)	De Rey et al. 1983 UO2(NO3)2*6H2O
		Dermal		237 M (mild lesion)		
Rat (Wistar)	once (EPICU)	Renal		85 F (proteinuria; minimal microscopic lesions in renal tubular epithelium)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt		85 F (unspecified decreased body weight gain)		

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form
				Less Serious (mg/kg)	Serious (mg/kg)	
Mouse (albino)	4 hr (EPICU)	Renal		948 F (moderate tubular degeneration)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt		948 (unspecified decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal		689 (proteinuria)		Orcutt 1949 UCl4
		Bd Wt		689 (10-20% decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal	450	616 (proteinuria)		Orcutt 1949 UO2(NO3)2*6H2O
		Bd Wt	450	616 (unspecified decreased body weight gain)		
Gn pig (NS)	4 hr (EPICU)	Renal		660 (proteinurea)		Orcutt 1949 UCl4
		Bd Wt		660 (10-20% reduction in weight gain)		
Rabbit (New Zealand)	once (EPICU)	Renal		618 (proteinuria)		Orcutt 1949 UO2F2
		Dermal	618			

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
Rabbit (New Zealand)	4 hr (EPICU)	Renal		344.1 (proteinuria)		Orcutt 1949 UCl5
		Dermal		344.1 (moderate skin irritation)		
Rabbit (New Zealand)	4 hr (EPICU)	Renal		666 (proteinuria)		Orcutt 1949 UO3
		Dermal	666			
Rabbit (New Zealand)	4 hr (EPICU)	Renal		195 (proteinuria)		Orcutt 1949 Na2U2O7
		Dermal	195			
Rabbit (New Zealand)	4 hr (EPICU)	Renal		169 (proteinuria)		Orcutt 1949 (NH4)2U2O7
		Dermal	169			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	410			Orcutt 1949 UO4
		Dermal	410			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	458			Orcutt 1949 UO2
		Dermal	458			

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)		LOAEL Serious (mg/kg)		Reference Chemical Form
Rabbit (New Zealand)	4 hr (EPICU)	Renal	147					Orcutt 1949 U3O8
		Dermal	147					
Rabbit (New Zealand)	4 hr (EPICU)	Renal		1.4	(proteinuria)			Orcutt 1949 UO2(NO3)2*6H2O
		Dermal		1.4	(moderate erythema)			
		Bd Wt	6	30	(decreased body weight gain)			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	98					Orcutt 1949 UF4
		Dermal	98					
Neurological								
Rabbit (New Zealand)	4 hr (EPICU)					1.4	(irritability, hyperactivity, upset equilibrium, rigidity of limbs, respiratory arrest)	Orcutt 1949 UO2(NO3)2*6H2O
INTERMEDIATE EXPOSURE								
Death								
Gn pig (NS)	4 wk 3 d/wk (EPICU)					379	(14% mortality)	Orcutt 1949 UO2(NO3)2*6H2O

Table 2-4. Levels of Significant Exposure to Uranium - Chemical Toxicity - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg)	LOAEL				Reference Chemical Form
				Less Serious (mg/kg)		Serious (mg/kg)		
Gn pig (NS)	4 wk 6 d/wk (EPICU)					47	(12% mortality)	Orcutt 1949 UO2(NO3)2*6H2O
Systemic								
Gn pig (NS)	4 wk 3-6 d/wk (EPICU)	Renal		47 mg/kg/ day	(proteinuria)			Orcutt 1949 UO2(NO3)2*6H2O
		Dermal		47	(skin irritation)			
		Bd Wt	47	161.2	(transitory weight loss)			
Rabbit (New Zealand)	5 wk 5 d/wk (EPICU)	Renal		2.3 mg/kg/ day	(proteinuria)			Orcutt 1949 UO2(NO3)2*6H2O
		Dermal				2.3	(severe dermal ulcers)	
		Bd Wt		2.3	(temporary weight loss)			

Bd Wt = body weight; d = day(s); EPICU = epicuticle; F = female; Gn Pig = guinea pig; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified; occup = occupational; wk = week(s); x = times

The highest NOAEL values and all reliable LOAEL values in each species and duration category for adverse systemic effects from chemical exposure to uranium by the dermal route are presented in Table 2-4.

Renal Effects. Rabbits, guinea pigs, rats, and mice dermally exposed to uranyl nitrate hexahydrate for 1 day showed proteinuria for up to 10 days, followed by recovery to control values. The degree of proteinuria did not correlate well with the applied dose of uranium. Rabbits had elevated blood NPN at doses over 270 mg U/kg. The animals that died from dermal exposure to uranium had microscopic renal damage typical of uranium poisoning. The kidneys of the animals that did not die were essentially normal, which may reflect repair of acute renal injury (Orcutt 1949). Chemically induced renal failure caused 100% mortality in male Wistar rats after 5 daily exposures to 237 or 1,928 mg U/kg/day as uranyl nitrate hexahydrate or ammonium uranyl tricarbonate, respectively, applied in a water-Vaseline® emulsion (De Rey et al. 1983). Deaths from renal failure were also reported in this study for male Wistar rats that received daily applications of 1,965 mg U/kg as uranyl acetate dihydrate for 1–11 days.

Dermal Effects. No human studies were located regarding the dermal effects of uranium; however, no dermal effects were reported in studies of uranium miners, millers, and processors.

In animal studies, application of 41 mg U/kg as uranium pentachloride to the shaved backs of New Zealand white rabbits resulted in mild skin irritation (Orcutt 1949). Dermally applied uranium was also damaging to the epidermis in other animal studies. Application of 56.4 mg U/kg as uranyl nitrate hexahydrate to another group of rabbits resulted in superficial coagulation necrosis and inflammation of the epidermis, while a dose of 4.2 mg U/kg as uranyl nitrate hexahydrate applied in single or multiple sites for 5 weeks resulted in severe dermal ulcers. No untreated controls were used in the 5-week study (Orcutt 1949). Moderate erythema was observed in male and female New Zealand white rabbits after single applications of 1.4 mg U/kg as uranyl nitrate hexahydrate to their uncovered clipped skins (Orcutt 1949). An applied dose of 2,670 mg U/kg as ammonium diuranate for 1–10 daily applications to the shaved backs of a group of rats resulted in mild lesions on the skin of the rats, while a dose of 237 mg U/kg as uranyl nitrate hexahydrate resulted in disrupted membranes in the cell, mitochondria, and cell nucleus, as revealed by transmission electron microscopy (TEM). Light microscopy revealed swollen and vacuolated epidermal cells and damage to hair follicles and sebaceous glands in the uranyl nitrate hexahydrate-treated animals (De Rey et al. 1983).

No dermal effects were seen following application of a single dose of 618 mg U/kg as uranyl fluoride, 666 mg U/kg as uranium trioxide, 195 mg U/kg as sodium diuranate, 198 mg U/kg as ammonium diuranate, 410 mg U/kg as uranium peroxide, 458 mg U/kg as uranium dioxide, or 147 mg U/kg as triuranium octaoxide in 50% aqueous solution to the shaved skin of New Zealand white rabbits (Orcutt 1949). No dermal effects were observed on the shaved backs of New Zealand white rabbits to which a single dose of 98 mg U/kg as a 65% concentration of the uranium tetrafluoride in lanolin was applied (Orcutt 1949). Similarly, application of 3,929 mg U/kg as uranyl acetate dihydrate or 2,103 mg U/kg as ammonium uranyl tricarbonate in water-Vaseline® emulsion to a 3 cm^2 shaved area of the uncovered backs of 20 male Wistar rats in 1–10 daily applications had no effect on the skin of the rats (De Rey et al. 1983).

Body Weight Effects. In animal studies, significant weight loss was reported in rats after the following dermal applications over a 3 cm^2 area: 3,948 mg U/kg as uranyl nitrate hexahydrate, 3,929 mg U/kg as uranyl acetate dihydrate, 2,103 mg U/kg as ammonium uranyl tricarbonate, or 2,670 mg U/kg as ammonium uranate to rats for 1–10 days (De Rey et al. 1983). Weight loss was also observed after single applications of 660 or 689 mg U/kg as uranium tetrachloride to guinea pigs, 616 or 948 mg U/kg as uranyl nitrate hexahydrate to mice, 85 mg U/kg as uranyl nitrate hexahydrate to rats, and 43 mg U/kg as uranyl nitrate hexahydrate to rabbits (Orcutt 1949).

Uranium (4.2 mg U/kg/day) applied as uranyl nitrate hexahydrate to the clipped backs of New Zealand white rabbits for 5 weeks also induced significant weight loss that peaked at 10–15 days after beginning treatment (Orcutt 1949). However, in several other animal studies, no changes in body weight in New Zealand white rabbits were reported following single dermal applications of 618 or 804 mg U/kg as uranyl fluoride, 344 mg U/kg as uranium pentachloride, 666 mg U/kg as uranium trioxide or uranyl fluoride, 344 mg U/kg as uranyl pentachloride, 195 mg U/kg as sodium diuranate, 198 mg U/kg as ammonium diuranate, 410 mg U/kg as uranium peroxide, 458 mg U/kg as uranium dioxide, or 147 mg U/kg as triuranium octaoxide (Orcutt 1949).

2.2.3.3 Immunological and Lymphoreticular Effects

No information was located regarding the effects of uranium on the immunological and lymphoreticular system in humans and animals following dermal exposure for any duration.

2.2.3.4 Neurological Effects

No studies were located for humans regarding neurological effects following dermal exposure to uranium compounds; however, such effects have not been observed in studies involving workers in uranium mining, milling, and production.

In animal studies, neurological signs observed in rabbits in a test in which single dermal doses of 1.4, 3, 6, 30, or 85 mg U/kg as uranyl nitrate hexahydrate were applied included irritability, hyperactivity, upset equilibrium, limb rigidity, and respiratory arrest at all doses tested (Orcutt 1949). The LOAEL value for this study is presented in Table 2-4.

2.2.3.5 Reproductive Effects

No studies were located for humans and animals that described reproductive effects following dermal exposure to uranium for any duration.

2.2.3.6 Developmental Effects

No studies were located regarding effects of uranium on development in humans or animals following dermal exposure for any duration.

2.2.3.7 Genotoxic Effects

No information was located regarding the toxicity of uranium to genetic material in humans or animals following dermal exposure for any duration of exposure. Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No information on the cancer effects in humans or animals following dermal exposure to uranium for all durations of exposure was located; however, such effects have not been observed in studies involving uranium mining, milling, and production.

2.3 TOXICOKINETICS

Overview. Absorption of uranium is low by all exposure routes (inhalation, oral, and dermal). Absorption of inhaled uranium compounds takes place in the respiratory tract via transfer across cell membranes. The deposition of inhalable uranium dust particles in the lungs depends on the particle size, and its absorption depends on its solubility in biological fluids (ICRP 1994, 1996) Estimates of systemic absorption from inhaled uranium-containing dusts in occupational settings based on urinary excretion of uranium range from 0.76 to 5%. A comprehensive review of the available data for a pharmacokinetic model used lung absorption factors of 2% to 4% for 3 month old children and 0.2% to 2% for adults, based on compound absorbability (ICRP 1996). Gastrointestinal absorption of uranium can vary from <0.1 to 6%, depending on the solubility of the uranium compound. Studies in volunteers indicate that approximately 2% of the uranium from drinking water and dietary sources is absorbed in humans (Leggett and Harrison 1995; Spencer et al. 1990; Wrenn et al. 1989), while a comprehensive review indicates that the absorption is 0.2% for insoluble compounds and 2% for soluble hexavalent compounds (ICRP 1996). Dermal absorption has not been quantified, but toxicity experiments in animals indicate that water-soluble uranium compounds are the most easily absorbed. Once in the blood, uranium is distributed to the organs of the body. Uranium in body fluids generally exists as the uranyl ion $(UO_2)^{2+}$ complexed with anions such as citrate and bicarbonate. Approximately 67% of uranium in the blood is filtered in the kidneys and leaves the body in urine within 24 hours; the remainder distributes to tissues. Uranium preferentially distributes to bone, liver, and kidney. Half-times for retention of uranium are estimated to be 11 days in bone and 2–6 days in the kidney. The human body burden of uranium is approximately 90 µg; it is estimated that 66% of this total is in the skeleton, 16% in the liver, 8% in the kidneys, and 10% in other tissues. The large majority of uranium (>95%) that enters the body is not absorbed and is eliminated from the body via the feces. Excretion of absorbed uranium is mainly via the kidney. The case of Gulf War veterans who were exposed to depleted uranium from inhalation, ingestion, and wounds, showed average urinary excretion, 7 years post exposure, of 0.08 µg U/g creatinine, with the highest rates around 30 µg/g (McDiarmad et al. 1999b).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The deposition of inhalable uranium dust particles in the various regions of the lungs (extrathoracic, tracheobronchial, and deep pulmonary or alveolar) depends on the size of the particles. Particles larger than 10 µm are likely to be transported out of the tracheobronchial region by mucocilliary action and

swallowed. Particles that are sufficiently small to reach the alveolar region (#10 µm AMAD) may transfer rapidly or slowly into the blood, depending on the solubility of the uranium compound. According to the ICRP (1996), a more soluble compound (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) is likely to be absorbed into the blood from the alveoli within days and is designated inhalation Type F (fast dissolution). A less soluble compound (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) is likely to remain in the lung tissue and associated lymph glands for weeks and is designated Type M (medium dissolution). A relatively insoluble compound (uranium dioxide, triuranium octaoxide) may remain in the lungs for years and is designated Type S (slow dissolution).

Analysis of excreta of active uranium mill crushermen exposed to ore dust indicated that 1–5% of uranium entering the lungs was absorbed systemically and excreted in the urine, and 95–99% was eliminated in the feces. Absorption could have taken place in the lungs or in the gastrointestinal tract from swallowed particles cleared from the lungs (Fisher et al. 1983). Uranium workers exposed to high levels of uranium dust had a very low lung burden of uranium, indicating that only a small fraction penetrates into the alveolar region (West and Scott 1969) and remains there without being cleared (or being very slowly cleared) via retrograde tracheobronchial mucus transport to the gastrointestinal tract, into lymph nodes, or dissolved into the circulating blood.

Estimates of absorption into the blood were derived from the excretion data of uranium mill workers (Wrenn et al. 1985). They estimated the daily mean absorption of inhaled uranium by mill workers at 24 µg U/day (0.34 µg U/kg for 70-kg reference man) based on measured excretion in feces and workplace ambient air concentrations. The absorption of uranium by these workers was estimated as 0.76% (range, 0.4–1.6%). Control subjects in a study of differential metabolism of ^{230}Th, ^{234}U, and ^{238}U inhaled in uranium ore dust included 3 retired uranium mill workers (4–14 years since last employment as uranium ore crushermen), and 3 volunteers who lived in uranium milling communities but had no uranium work history. Two consecutive 24-hour urine and fecal collections were obtained and analyzed for ^{234}U and ^{238}U. The apparent total intakes of uranium of these individuals ranged from 11 to 18 µg U/day for the controls and from 5.3 to 71 µg U/day for the retirees. Although large compared to uranium intakes estimated for city dwellers, the uranium intakes of these individuals are not unreasonable because uranium in potable waters and locally grown foods tends to be higher in uranium mining and milling

communities. The mean uranium absorption calculated for the controls (0.82%; range, 0.6–1%) was not significantly different from that calculated for the retired uranium workers (0.94%; range, 0.55–1.6%) (Wrenn et al. 1985).

Urinary excretion data was used to estimate the absorption of uranium by workers accidentally exposed to uranium hexafluoride (Fisher et al. 1990). Estimated airborne concentrations were 20 mg uranium hexafluoride/m^3 for a 1-minute exposure and 120 mg uranium hexafluoride/m^3 for a 60-minute exposure (15.2 and 91 mg U/m^3, respectively) (USNRC 1986). Initial intakes of workers involved in the accident ranged from 470 to 24,000 µg uranium.

Higher absorption of uranium occurred in animal studies using aerosols of purified uranium compounds. In these studies, as in human studies, the solubility of the uranium compound and the size of the inhaled particles determined absorption. Reported absorption of the inhaled dose was 18–40% in rats and 20–31% in guinea pigs for uranium hexafluoride (Leach et al. 1984) and 23% for uranium trioxide in dogs (Morrow et al. 1972).

2.3.1.2 Oral Exposure

Experimental studies in humans consistently show that absorption of uranium by the oral route is less than 5%. Reported fractional absorptions include a range of 0.005–0.05 (0.5–5%) in a group of four males ingesting 10.8 mg uranium in a soft drink (Hursh et al. 1969), less than 0.0025–0.04 in a group of 12 volunteers given drinking water high in uranium (Wrenn et al. 1989), and 0.005–0.05 in another drinking water study (Harduin et al. 1994). Similar results were obtained in dietary balance studies (Leggett and Harrison 1995; Spencer et al. 1990; Wrenn et al. 1989). A review of human data conducted by the ICRP determined that a fractional absorption of 0.02 for soluble compounds and 0.002 for insoluble compounds should be used in modeling the kinetics of dietary uranium in humans (ICRP 1995).

In animal studies, absorption generally increases with increasing solubility of the compound, being greatest for uranium ingested as uranyl nitrate hexahydrate, uranium hexafluoride or uranyl fluoride, about half as great for uranium tetroxide or uranium trioxide, and 1–2 orders of magnitude lower for uranium tetrachloride, triuranium octaoxide, and uranium tetrafluoride (ICRP 1995). Increased absorption of uranium has been demonstrated in neonatal rats and pigs (ICRP 1995). Fractional

absorption in 2-day-old rats given uranyl nitrate was estimated as 0.01–0.07, two orders of magnitude greater than for adults (ICRP 1995).

Evidence from several animal studies showed that the amount of uranium absorbed from the gastrointestinal tract was about 1% (Harrison and Strather 1981; Larsen et al. 1984; LaTouche et al. 1987; Maynard et al. 1953; Sullivan 1980a). A range of gastrointestinal absorption rates of 0.038–0.078% has been estimated by others based on data from a 2-year study in which rats were fed diets containing 0.05–0.5% of soluble uranium compounds (uranyl fluoride or 0.5–2% of uranyl nitrate). The rate of absorption appeared to be independent of concentration of uranium in the diet (Wrenn et al. 1985). Absorption factors in rats that were exposed by gavage to doses of ^{233}U-uranyl nitrate hexahydrate (where this anthropogenic radionuclide provided increased sensitivity without competition with natural isotopes) increased 3.4 times over normal in rats that were iron-deficient (Sullivan and Ruemmler 1988), doubled in rats that were fasted (Sullivan et al. 1986), and increased 3.6 times in neonates as compared to adults (Sullivan 1980b). Adult baboons (fed normally) absorbed about 0.5%, whereas fasted baboons absorbed an average of 4.5% (Bhattacharyya et al. 1989). Consistent with the results in baboons, fed and 24-hour fasted male B6CF$_1$/ANL mice absorbed 0.069% and 0.80%, respectively (Bhattacharyya et al. 1989).

2.3.1.3 Dermal Exposure

Absorption of uranium through the skin has not been characterized in humans. Dermal absorption in animal models can be inferred from the appearance of toxicity in mice, rats, rabbits, and guinea pigs after dermal exposure to uranium compounds (Orcutt 1949). Absorption was also shown to occur through the conjunctival sac of the eye.

Electron microscopy and X-ray microanalytical methods showed that uranium as uranyl nitrate hexahydrate penetrated the stratum corneum within 15 minutes and accumulated in the intracellular space between the viable epidermis and the stratum corneum (De Rey et al. 1983). As is the case with inhalation and oral absorption, water solubility is an important determinant of absorption, and no penetration was observed with the insoluble compounds uranium dioxide, uranyl acetate, or ammonium diuranate. After 48 hours, uranium applied as uranyl nitrate was no longer found in the skin and toxicity developed, indicating that the uranium had been absorbed into the blood.

2.3.2 Distribution

Absorbed uranium is found in all human tissues, but preferentially deposits in bone and kidney, regardless of the route of exposure (ICRP 1995, 1996). Although uranium also distributes significantly to liver, this organ is not a major repository for uranium; however, for modeling purposes, tissue contents are often normalized to liver concentration because the latter is reported in almost all studies of uranium biokinetics. The normal adult's body burden is considered to be approximately 90 µg. It is estimated that about 66% of this total is in bone, 16% in the liver, 8% in the kidneys, and 10% in other tissues (ICRP 1979, 1995, 1996). It is not known if maternal bone stores of uranium (like those of calcium and lead) are mobilized during pregnancy and lactation. Uranium can cross the placenta after parenteral administration in animals; no information was located on distribution of uranium in breast milk for either humans or animals.

2.3.2.1 Inhalation Exposure

Autopsy data from individuals occupationally exposed to uranium indicates that bone is the primary site of long term retention of absorbed uranium (ICRP 1995). Inhalation exposure may also result in some retention of insoluble uranium particles in the lungs. An evaluation of the postmortem data from a uranium worker who had inhaled a total of 220 mg (147 pCi) uranium over a 3-year period found 11 µg (7 pCi) uranium in the lungs 13 years after the end of exposure. The total calculated dose equivalent from the inhaled uranium was 35 rem (0.35 Sv) (Keane and Polednak 1983).

In a comprehensive study of tissues from two long-time residents of New Mexico without known occupational exposure, the skeleton was the primary depot for uranium (Kathren 1997). Approximately 80 soft tissue samples and 90 bone samples were analyzed from each subject. The mean uranium concentrations in bone were 4.8 and 5.8 ng/g wet weight for the two subjects, respectively. Highest concentrations of uranium in soft tissues were in the tracheobronchial and other pulmonary related lymph nodes indicating uranium-bearing particulate clearance from the lungs. Concentrations in pulmonary lymph nodes ranged from 16–28 ng/g in one individual to 29–259 ng/g wet weight in the other.

Urinary excretion data were used in a kinetic model to estimate the maximum uranium kidney concentrations of workers accidentally exposed to uranium hexafluoride (Fisher et al. 1990). Initial intakes of workers involved in the accident ranged from 470 to 24,000 µg uranium. The model estimated the

maximum kidney concentrations in the workers as ranging from 0.048 to 2.5 µg U/g in kidney tissue; renal toxicity was not observed in any of the workers (Fisher et al. 1990).

In animals, uranium that has been absorbed from the lungs leaves the blood very quickly for distribution to body tissues. The insoluble compounds (uranium tetrafluoride, uranium dioxide) were found to accumulate in the lungs and lymph nodes with the amount retained dependent on the exposure concentration and duration. In a continuous exposure study, more than 90% of the uranium retained at the end of the first year of exposure to a uranium dioxide aerosol was cleared by the end of the second year despite continued inhalation of uranyl nitrate. All of the uranium retained following one year of inhalation of uranyl hexafluoride was cleared by the end of the second year. For uranyl nitrate inhalation, no retention was found in the soft tissues. Uranium has also been shown to accumulate in the tracheo-bronchial lymph nodes, lungs, bones, and kidneys of rats, dogs, and monkeys exposed to uranium dioxide at 5 mg U/m^3 for 1–5 years. Total radiation absorbed dose in dog lungs was around 600 rads (6 Gy). Up to 7,000 rads (70 Gy) were absorbed by monkey lymph nodes (Leach et al. 1973). In rats exposed to yellowcake, the U_3O_8 portion of the yellowcake cleared from the lung with a half-time of 110–240 days (Damon et al. 1984). Mice given inhaled doses of U_3O_8 equivalent to about 0.2 mg U/kg exhibited uranium tissue distribution (in µg/g tissue) as follows: lung, 6.05; liver, 0.051; spleen, 1.45; kidney, 0.536; tibia, 0.731; urine, 0.519; and feces, 2.20 (Walinder 1989). In an inhalation study using highly enriched uranium dioxide particles (92.8% ^{235}U), rat lungs were found to clear the uranium particles at a rate of 0.28% per day over a period of 720 days. At 720 days postexposure, 82% of the uranium remained in the lungs and thoracic lymph nodes of the rats. The highest mass of extrapulmonary uranium dioxide was detected in rats sacrificed up to 11 days postexposure. This was mainly found in the intestinal tract and the carcass. The authors found that the pulmonary clearance rate of highly enriched uranium dioxide particles was about the same as the clearance rate for natural or unenriched uranium dioxide particles (Morris et al. 1990), as would be expected since they are the same chemical compound.

One site of deposition for the soluble compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) in animals was the skeleton, but accumulation was not seen in bone at levels below 0.25 mg U/m^3 over a period of 2 years in rats exposed to soluble compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) in one study. The insoluble compounds (uranium hexafluoride, uranium dioxide) were found to accumulate in the lungs and lymph nodes after the inhalation exposure. For uranyl nitrate exposure, no retention was found in the soft tissues. Accumulation of uranium was also

found in the skeleton (Stokinger 1953). The amount distributed in the skeleton has been reported to be 23–45% of the intake in dogs (Morrow et al. 1972); 28–78% in rats (Leach et al. 1984); and 34–43% in guinea pigs (Leach et al. 1984). A biological half-time of 150–200 days (Ballou et al. 1986) or 70 days (Morrow et al. 1982) in the skeleton has been reported following inhalation exposure to soluble uranium compounds (e.g., uranium hexafluoride).

A 5-year exposure of Beagle dogs and monkeys, and a 1-year exposure of rats, to 5.8 mg uranium dioxide/m^3 (5.1 mg U/m^3) as uranium dioxide dust (AMAD=1 μm) resulted in rapid lung buildup during the first few months, which approached maximal values of 2, 3.6, and 0.8 mg U/g in dogs, monkeys, and rats, respectively, at the end of year 1. Buildup in the tracheobronchial lymph nodes reached peak values in year 4 of 50–70 mg U/g in both dogs and monkeys. For each, the peak radiation dose rates reached 1.8 and 3.3 rads/week (0.018 and 0.033 Gy/week) to lungs, and 55 and 64 rads/week (0.55 and 0.65 Gy/week) to lymph nodes, while the total radiation dose for the 5 years approached 500 and 900 rads (5 and 9 Gy) to lungs and 10,000 rads (10 Gy) to the lymph nodes. Renal damage was not observed in either the dog or monkey, but fibrosis was found in the monkey lung and both necrosis and fibrosis were found in the dog and monkey lymph nodes. It was not clear whether the damage was chemically or radiologically induced, but the presence of lung and lymph node damage in the absence of renal effects was suggestive to the authors of long-term radiation damage (Leach et al. 1970). A reevaluation of the study data also showed a rapid accumulation of uranium in the lungs and tracheobronchial lymph nodes during the first few months of exposure. The accumulation in these organs was highest (0.8 mg/g in lungs and 1.5 mg/g in lymph nodes) at the end of 1 year of exposure. The uranium content in the lungs decreased with a half -time of approximately 480 days. In the lymph nodes, uranium depletion showed a trend similar to the lungs in dogs exposed for 2 and 5 years and a biphasic pattern in dogs exposed for 1 year. Comparatively low levels of uranium were found in the kidney, femur, liver, and spleen, and these decreased with time (Leach et al. 1973).

In other studies, no significant accumulation was found in the spleen or liver of rats, dogs, or guinea pigs (Ballou et al. 1986; Diamond et al. 1989; Leach et al. 1973, 1984; Morrow et al. 1972; Wrenn et al. 1987).

2.3.2.2 Oral Exposure

Uranium levels have been measured in tissues from humans, with no occupational exposure where the source of uranium was assumed to be dietary and environmental.

In a comprehensive study of tissues from two long-time residents of New Mexico, the skeleton was the primary depot for uranium (Kathren 1997). Approximately 80 soft tissue samples and 90 bone samples were analyzed from each subject. The mean uranium concentrations in bone were 4.8 and 5.8 ng/g wet weight for the two subjects, respectively. Highest concentrations of uranium in soft tissues were in the tracheobronchial and other pulmonary related lymph nodes, indicating uranium-bearing particulate clearance from the lungs. Concentrations in pulmonary lymph nodes ranged from 16–28 ng/g in one individual to 29–259 ng/g wet weight in the other. An unexpectedly high concentration was found in the thyroid of one subject. In both subjects, uranium was widely distributed among the soft tissues; liver concentrations were lower than those in the kidney (approximately 0.1 ng/g and 0.9 ng/g wet weight, respectively).

The concentrations of uranium in human blood from New York City donors averaged 0.14 mg U/kg in both whole blood and red cells, compared to values ranging from <0.04 to 86 mg U/kg globally (Fisenne and Perry 1985). The median concentrations of uranium in the lungs, liver, kidneys, and vertebra from New York City residents among all age groups were reported to be 0.33, 0.13, 0.32, and 0.29 mg U/kg, respectively (Fisenne and Welford 1986). The concentration of uranium in human fat with no known occupational exposure was 0.6 ng/g (EPA 1985).

In an evaluation of two human skeletal tissues, it was observed that the sacrum contained the highest concentrations of ^{238}U and ^{234}U (4.9 mBq/g ash) (0.13 pCi/g ash) (0.20 µg/g ash). The concentration of ^{238}U was lowest (0.1 mBq/g ash) (0.0027 pCi/g ash) (0.004 µg/g ash) in the right femur (Singh et al. 1987b). In the United Kingdom, the uranium concentration in wet bone was reported to be 3 mg U/kg (2 nCi U/kg) (Fisenne and Welford 1986).

Data on laboratory animals indicate that a substantial portion of uranium leaving the blood may initially distribute throughout soft tissues, but a few days after absorption or injection into the blood, most of the systemic content is found in the kidneys and skeleton (Bhattacharyya et al. 1989; ICRP 1995).

In animals, a substantial fraction of plasma uranium is associated with the ultrafilterable low-molecular-weight fraction, and the remainder is weakly associated with transferrin and other plasma proteins. Data on baboons indicate that 50% or more of the uranium in blood is associated with the red blood cells during the period 10–1,000 hours after injection. These data have been interpreted to mean that about 0.7% of the uranium leaving the plasma attaches to red blood cells and is returned to plasma with a half-time slightly greater than 1 day (ICRP 1995).

In animals, absorbed uranium is osteotropic, accumulating largely on the surface of all types of bone of the animals. Eventually, the uranium on the bone surface diffuses into the mineral portion of the bone. Autoradiography provides confirming evidence that, in the long term, uranium is a bone volume seeker (Wrenn et al. 1987). Kinetic models of uranium distribution predict that, for the short-term, uranium distributes to the bone surface and bone marrow while the deep bone is the long-term depot (Sontag 1986). These results suggest that the macro distribution of uranium in the human skeleton is not uniform.

In some ways, the skeletal behavior of uranium is quantitatively similar to that of alkaline earths. It is known that the uranyl ion (UO_2^{2+}) exchanges with Ca^{2+} on the surfaces of bone mineral crystals, although it does not participate in crystal formation or enter existing crystals. The early distribution of uranium in different parts of the skeleton is similar to that of calcium. Uranium initially deposits on all bone surfaces but is most highly concentrated in areas of growth. Depending on the microscopic structure of the bone of each species, uranium on bone surfaces may gradually diffuse into bone volume; such diffusion has been observed in dogs but not in rats or mice. As with calcium, a substantial portion of uranium deposited in bone is lost to plasma by processes that occur more rapidly than bone resorption (see Section 2.3.5). In human subjects injected with uranium, an estimated 80–90% of the original skeletal deposition was lost from bone over the first 1.5 years (ICRP 1995).

In a study with female mice exposed orally in feed to uranyl nitrate hexahydrate at a dosage of 462 mg U/kg/day for 36–44 weeks, average uranium accumulation was 6 µg per pair of kidneys, 46 µg/g bone and 0–0.5 µg in whole liver, respectively. No significant organ accumulation was found for the lower dose levels (Tannenbaum and Silverstone 1951). Maximal concentrations of 77 µg per pair of kidneys and 216 µg/g in bone were estimated at 50 weeks in male mice that were orally exposed to uranyl nitrate hexahydrate at 925 mg U/kg/day for 48 weeks. One mouse with small kidneys showed levels of 395 µg/pair of kidneys and 1,440 µg/g bone (Tannenbaum and Silverstone 1951). Average uranium

accumulation in the kidneys and bone of male mice exposed to uranyl fluoride orally at 452 mg U/kg/day for 28 weeks was 33 µg/pair of kidneys and 145 µg/g bone at 20 weeks (Tannenbaum and Silverstone 1951). Maximal concentrations of 6 µg/pair of kidneys at 50 weeks and 29 µg/g bone at 14 weeks were found in female mice given oral uranium tetrachloride at 978 mg U/kg/day for 48 weeks (Tannenbaum and Silverstone 1951).

The insoluble compounds of uranium accumulated to a lesser extent in tissues. Only small amounts of uranium were found in the kidneys (3–9 µg/pair of kidneys) of female mice that were exposed orally to uranium tetrafluoride at 4,437 mg U/kg/day for 48 weeks. No uranium was found in the bone (Tannenbaum and Silverstone 1951). Only small amounts of uranium were found in kidney (1–3 µg/pair of kidneys) of female mice that were exposed orally to triuranium octaoxide at 1,655 mg U/kg/day for 48 weeks. No uranium was found in the bone (Tannenbaum and Silverstone 1951).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of uranium after dermal exposure in humans or animals.

2.3.2.4 Other Routes of Exposure

Intravenously injected uranium is rapidly taken up by the tissues or excreted in the urine (ICRP 1995). Typically, 25% of intravenously injected uranium (as uranyl nitrate) remained in blood of human subjects after 5 minutes, 5% after 5 hours, 1% after 20 hours, and less than 0.5% after 100 hours although inter-subject variation was high (Bassett et al. 1948; Bernard and Struxness 1957). Measurements of systemic distribution of uranium made at autopsy in one terminally ill human given a single intravenous injection of uranium indicated that the skeleton, kidneys, and other soft tissues after 2.5 hours contained about 10, 14, and 6%, respectively, of the dose. Distribution data taken from another human subject 18 hours after a single intravenous injection uranium showed that the bones, kidneys, and other soft tissues contained about 4–13%, 6%, and 4%, respectively, of the amount injected. At 566 days post-injection, uranium distribution in the skeleton, kidneys, and other soft tissues declined to about 1.4, 0.3, and 0.3%, respectively.

The distribution of uranium metal implanted in muscle has been investigated in rats (Pellmar et al. 1999a). In these experiments, pellets of depleted uranium were implanted into the gastrocnemius muscle

and uranium levels were measured in kidney, muscle, liver, spleen, brain, serum and bone at 1 day and at 6, 12, 18 months after implantation. Within 1 day uranium was measurable in kidney and bone but not in the other tissues. At later time points, significant amounts of uranium were found in the other tissues, although levels were always highest in the kidney and bone.

2.3.3 Metabolism

Uranium is usually found in compounds which can be metabolized and recomplexed to form other compounds. In body fluids, tetravalent uranium is likely to oxidize to the hexavalent form followed by formation of uranyl ion. Uranium generally complexes with citrate, bicarbonates, or protein in plasma (Cooper et al. 1982; Dounce and Flagg 1949; Stevens et al. 1980). The stability of the carbonate complex depends on the pH of the solution, which will differ in different parts of the body (BEIR IV 1988). The low-molecular-weight bicarbonate complex can be filtered at the renal glomerulus, and be excreted in urine at levels dependent on the pH of the urine. The uranium bound to the protein (primarily transferrin) is less easily filtered and is more likely to remain in blood. In the blood, the uranyl ion binds to circulating transferrin, and to proteins and phospholipids in the proximal tubule (Wedeen 1992).

2.3.4 Elimination and Excretion

Two-thirds of uranium, intravenously injected as uranyl nitrate in human subjects was typically excreted in urine in the first 24 hours. Approximately 10% more was excreted over a period of 5 days. Fecal excretion accounted for less than 1% of the excretion (ICRP 1995).

2.3.4.1 Inhalation Exposure

In a study of 7,231 uranium workers, the urinary concentration of uranium ranged from 5 µg/L in 4,556 workers to more than 100 µg/L in 32 workers. Samples were taken weekly over a 6-year period. Among a control group of 600 non-uranium workers, none had urinary uranium concentrations that exceeded 40 µg/L. The author concluded that urinary uranium concentrations greater than 100 µg/L are definitely indicative of recent absorption, and that pathological albuminuria is rare, except when the urinary uranium concentration exceeds 1,000 µg/L. Albuminuria, when seen, was transient, and did not persist (Butterworth 1955).

Urinary excretion in crushermen (about 0.2 nCi/day [7 Bq/day][0.3 mg/day]) is about 1/100th of fecal excretion (about 13.5 nCi/day [500 Bq/day][20 mg/day]). The activity of ^{234}U in urine was slightly higher than that of ^{238}U. Active crushermen excreted higher levels of ^{234}U, ^{238}U, and ^{230}Th than retired crushermen or controls (Fisher et al. 1983). Most of the inhalation doses of female employees at the Oak Ridge plant were excreted in the feces, indicating that ciliary action in the lungs, followed by fecal excretion, was an important mechanism of body clearance (West and Scott 1969).

Zhao and Zhao (1990) reported on the excretion of uranium in an occupationally exposed worker. A 23-year old man who weighed 60 kg, dressed in protective clothing, mask, and gloves, was accidentally exposed to pure uranium tetrafluoride powder for 5 minutes. The uranium tetrafluoride powder cloud was reported to contain natural uranium. Urinary excretion was reported as 112 µg/L or 156.8 µg in the first 24 hours, gradually increasing through post-accident day 60 and returning to normal at about post-accident day 1,065. The total urinary excretion of uranium through day 1,065 was calculated to be 86.7 mg. The excretion data was used to calculate total absorption and kidney content by use of a kinetic model (ICRP 1979). The kidney content on post-accident day 1 was reported as 804.2 µg or approximately 2.6 µg/g of kidney.

The biological half-time of uranium dioxide in human lungs (occupational exposure) at German fuel fabrication facilities was estimated to be 109 days. Body burden measurements of uranium taken from 12 people who handled uranium oxides for 5–15 years were used for this determination. Twice a year for 6 years, a urinalysis was conducted on workers exposed to uranium. *In vivo* lung counting was performed on the last day before and the first day after a holiday period. Levels of uranium in feces were measured during the first 3 days and the last 3 days of a holiday period and the first 3 days after the restart of work. For some employees, the levels of uranium in feces was measured during 3–4 days one-half year after the holiday period (Schieferdecker et al. 1985).

In animals, most of absorbed uranium is excreted in urine. Inhaled larger particles ($10 µm) are transported out of the respiratory system by mucocilliary action, then swallowed, and eliminated in the feces (Ballou et al. 1986; Downs et al. 1967; Morrow et al. 1982). Deposition sites of inhaled aerosols, and hence the clearance kinetics, are determined in part by particle size of the inhaled particles. As the AMAD increases, the amount deposited in the upper respiratory tract increases, and the amount deposited in the deep respiratory tracts of the lungs decreases. This study used both ^{232}U and ^{233}U dusts. The ^{233}U dust deposition in the upper respiratory tract increased from 21 to 62% of the total

amount of dust deposited with increasing particle size; deposition in the deep lung decreased from 22 to 7% with increasing particle size. The ^{232}U dust deposition in the upper respiratory tract increased from 10 to 32% with increasing particle size; deposition in the deep lung decreased from 23 to 9% with increasing particle size. The differences were less marked for ^{232}U dust, presumably, because the particle size was much more uniform than that for the ^{233}U dust. A large amount of the initial lung burden was preferentially cleared via the feces following clearance from the upper respiratory tract to the gastro-intestinal tract (higher fecal excretion with higher AMAD) by mucocilliary action. Urinary excretion was 25–50% of initial lung burden on day 1; less with larger particles. By day 7, 25–80% of the uranium uptake was cleared in urine; most of the uranium was eliminated in the feces (Ballou 1986). In one study with rats, most of the inhaled uranium, as uranium dioxide, was excreted in the urine. In dogs, less than 10% was excreted in feces (presumably cleared by mucocilliary action) (Cooper et al. 1982). About 60% of the retained uranium, as uranyl nitrate hexahydrate (Ballou et al. 1986), uranium hexafluoride (Leach et al. 1984), and uranium trioxide (Morrow et al. 1982), was excreted in urine within 1 day in other studies with rats, dogs, and guinea pigs. Most of the retained uranium in rats exposed via intra-tracheal intubation with uranium dioxide or uranyl nitrate hexahydrate was excreted in the urine. Less than 10% was excreted in feces (presumably cleared by mucocilliary action) (Cooper et al. 1982). The fraction of insoluble compounds (uranium tetrafluoride, uranium dioxide) retained in the lungs and lymph nodes was independent of the exposure concentration. More than 90% of the uranium retained at the end of the first year of exposure to uranium dioxide was cleared by the end of the second year despite continued exposure to uranyl nitrate hexahydrate. All of the uranium retained following 1 year of exposure to uranium tetrafluoride was cleared by the end of the second year. For uranyl nitrate hexahydrate exposure, no retention was found in the soft tissues (Stokinger 1953).

Once deposited in the lungs, uranium compounds clear from the various biological compartments by solubility. The ICRP lung model recognizes three clearance classification types: F, M, and S. Type F compounds (uranium hexafluoride, uranyl fluoride, uranium trioxide, possibly uranium tetrafluoride, possibly triuranium octaoxide) show 100% absorption with a half-time of 10 minutes. Type M compounds (uranyl nitrate, ammonium diuranate, possibly uranium tetrafluoride, possibly triuranium octaoxide) show 10% absorption with a half-time of 10 minutes, and 90% with a half-time of 140 days, and about 70% of the material in the alveoli eventually reached body fluid. Type S compounds (uranium dioxide) show 0.1% absorption with a half-time of 1 minute, and 99.9% with a half-time of 7,000 days,

and 10% of that deposited in the alveoli reaches body fluid (ICRP 1996). The half-time of uranium in the lungs has also been calculated to be 1–5 days for soluble compounds like uranyl nitrate hexahydrate in rats (Ballou et al. 1986), ammonium diuranate in hamsters (Stradling et al. 1984), and uranyl fluoride in dogs (Morrow et al. 1982). It is longer for the less soluble uranium dioxide: 141–289 days in rats (Downs et al. 1967) and 480 days in dogs (Leach et al. 1973). In the kidney, uranium selectively accumulates in the proximal tubule with a biological half-time of about 1 week (Wedeen 1992). The half-time of uranyl fluoride in the kidneys has been reported to be 2–5 days in rats (Diamond et al. 1989) and 9 days in dogs. In dogs, less than 1% of the uranium remained in the kidneys after 30 days (Morrow et al. 1982).

2.3.4.2 Oral Exposure

The available evidence on the excretion of ingested uranium suggests that most ($95%) is excreted in the feces, and the remainder in urine (Wrenn et al. 1985). Urinary uranium excretion rates from nonoccupationally exposed persons in 3 villages near uranium mining and refining facilities and a control village in Japan ranged from <0.02–0.24 mg U/day per person and <0.02–0.04 mg U/day per person, respectively (Masuda 1971). The half-time in the kidneys has been estimated to be 1–6 days for 99% of the uranium in the kidneys and 1,500 days for the remainder (ICRP 1979). Most of the uranium doses, given as 900 mL of water containing 90 pCi (3.3 Bq) ^{234}U and 90 pCi (3.3 Bq) ^{238}U (180 pCi or 6.6 Bq uranium) to drink over a period of 6 hours, was excreted in feces within 2 days (Singh and Wrenn 1987). Four volunteers who ingested 10.8 mg of uranium mixed with Coca Cola excreted the uranium in both feces and urine over a 25-day period (Hursh et al. 1969). Urinary excretion after oral exposure is generally low and has been estimated as 2% of total excretion (Spencer et al. 1990).

Animal studies have shown that most ingested uranium (99%) is not absorbed in rats, but is eliminated in the feces without being cycled through the bile. In rats, most of the absorbed uranium leaves the body within a few days in urine; half is excreted in 2–6 days (Durbin and Wrenn 1975), and 98% within 7 days (Sullivan 1986). About 95% of the uranium in the kidneys of rats is excreted in urine within 1 week, and very little remains in any other organ (LaTouche et al. 1987; Sullivan 1980a, 1986).

Data from parenteral studies provide further indication that uranium retention in animal kidneys is described by a 2-compartment exponential curve. Reported biological half-times for the compartments

are 2 and 50–60 days (Diamond et al. 1989), 2 and 13 days (Bentley et al. 1985), or 3 and 103 days (Wrenn et al. 1986).

2.3.4.3 Dermal Exposure

No studies were located describing the excretion of uranium following dermal exposure in humans or animals.

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

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen

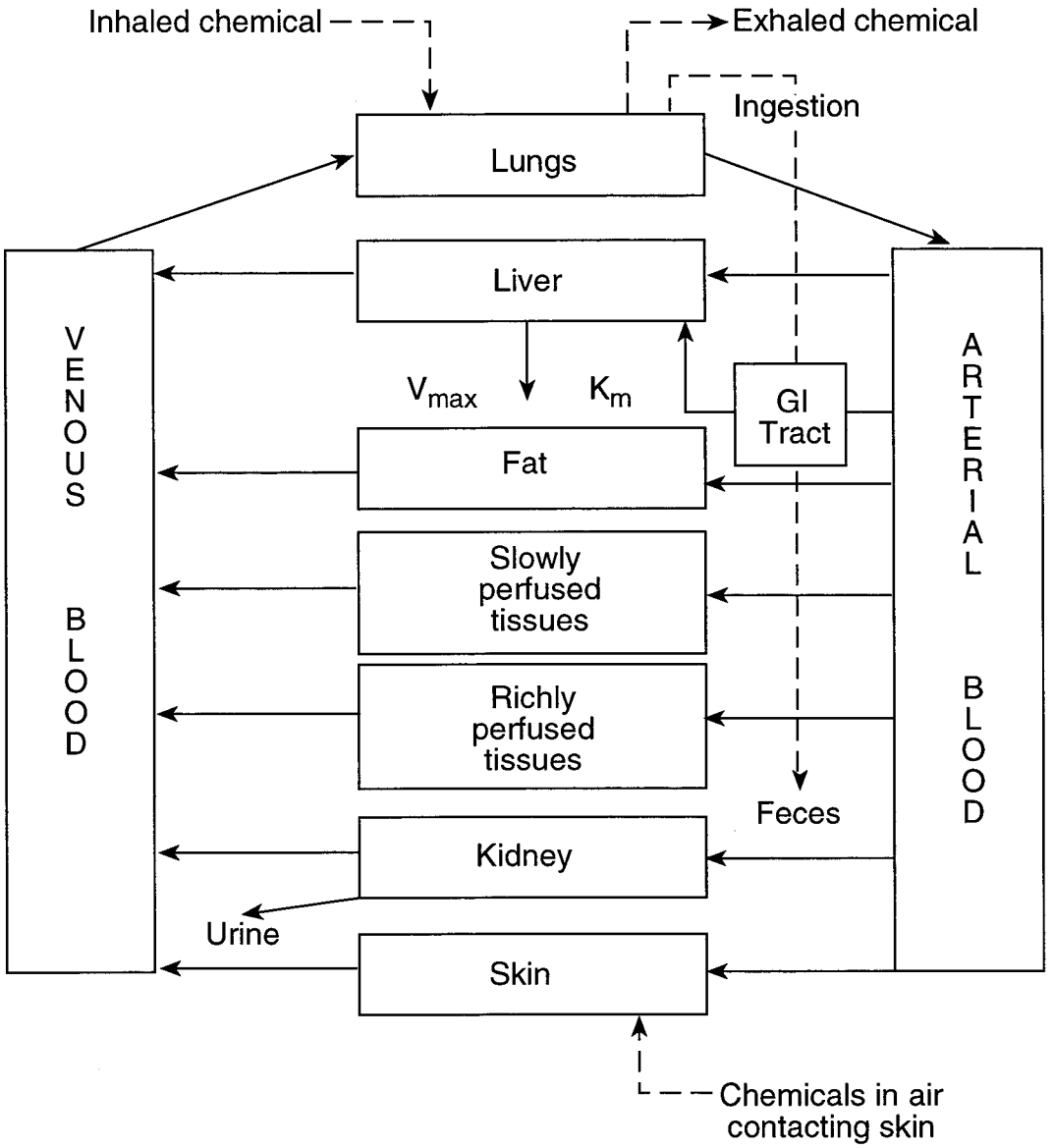
1994; Leung 1993). PBPK models for a particular chemical substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. This simplification, however, is desirable if the uptake and disposition of the chemical substance(s) is adequately described because data are often unavailable for many biological processes and using a simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance and, thus, model validation is important.

PBPK models improve the pharmacokinetic extrapolation aspects of the risk assessment process, which seeks to identify the maximal (i.e., safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically based means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model. The overall results and individual PBPK models are discussed in this section in terms of their use in risk assessment; tissue dosimetry; and dose, route, and species extrapolations.

The ICRP (1994, 1996) developed a Human Respiratory Tract Model for Radiological Protection which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to uranium. The ICRP (1995) also developed a biokinetic model for human oral exposure that applies to uranium. Two other compartmental models (Fisher et al. 1991; Sontag et al. 1986) are also described below. The National Council on Radiation Protection and Measurement (NCRP) has also developed a respiratory tract model for inhaled radionuclides (NCRP 1997). At this time, the NCRP recommends the use of the ICRP model for calculating exposures for radiation workers and the general public. Readers interested in this topic are referred to NCRP Report No. 125; *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (NCRP 1997). In the appendix to the report, NCRP provides the animal testing clearance data and equations fitting the data which supported the development of the human model.

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

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

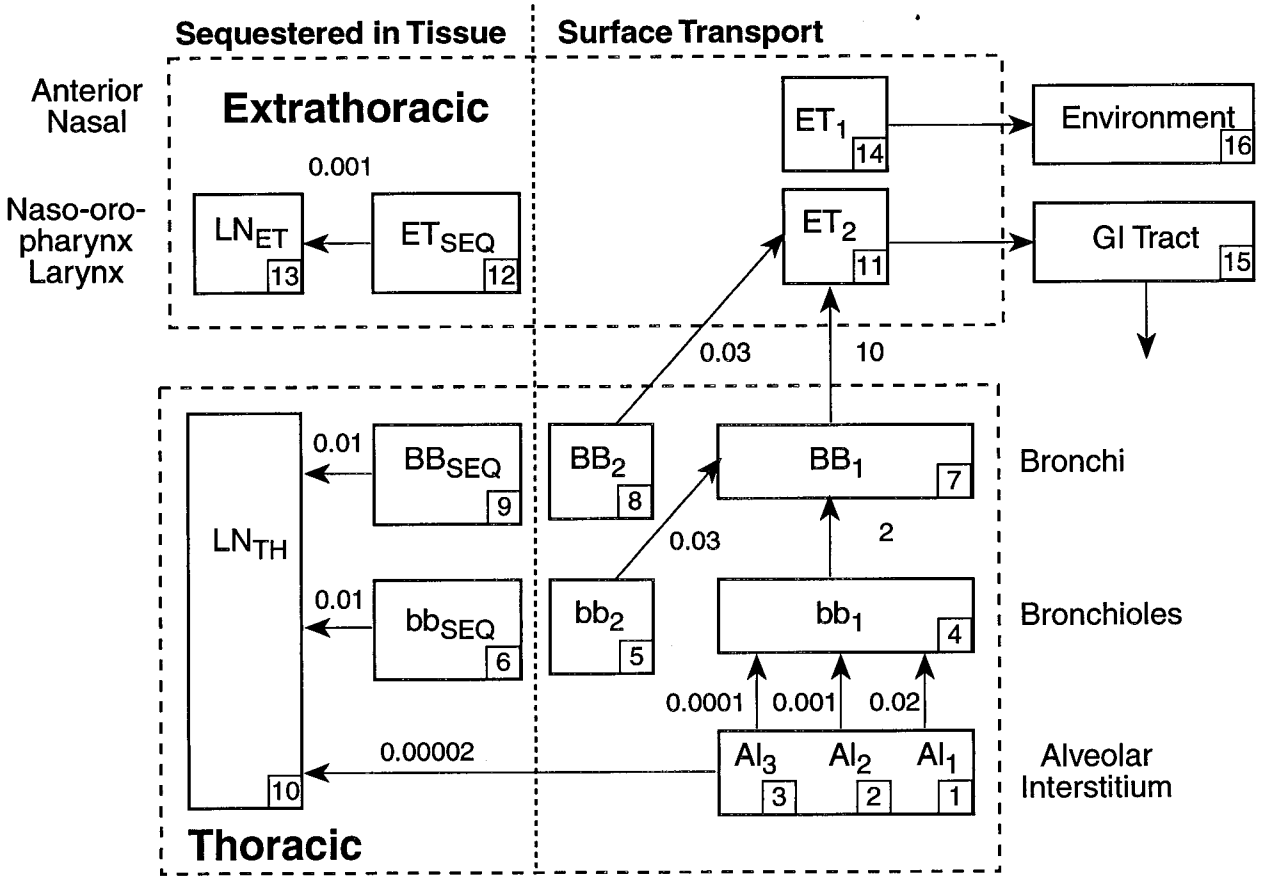
Deposition. The ICRP has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region. ICRP provides inhalation dose coefficients which can be used to estimate the committed equivalent and effective doses to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility, a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particles containing uranium, but was developed for a wide variety of radionuclides and their chemical forms.

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

For extrathoracic deposition, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 2-5 provides reference respiratory values for the general Caucasian population under several levels of activity.

Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. Figure 2-6 presents the compartmental model and is linked to the deposition model

Figure 2-5. Respiratory Tract Compartments in Which Particles May be Deposited



Size of arrow represents relative deposition rate

Source: ICRP 1994

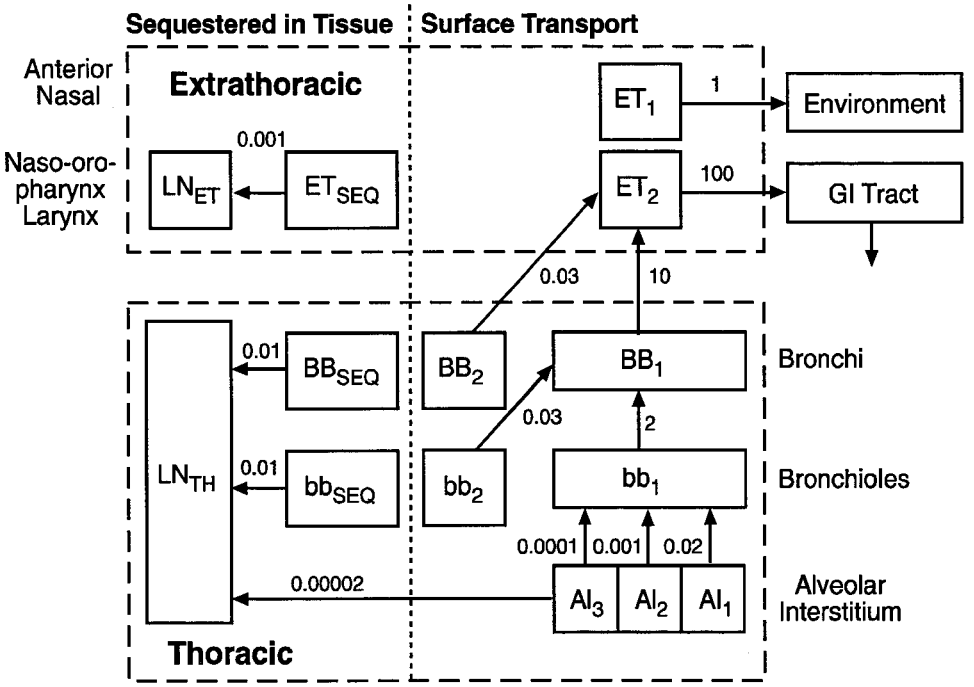
Table 2-5. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

Activity:		Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
Maximal workload (%):		8			12			32			64		
Breathing paramters:[b]		V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})
Age	Sex												
3 mo		0.04	0.09	38	N/A	N/A	N/A	0.07	0.19	48	N/A	N/A	N/A
1 y		0.07	0.15	34	0.1	0.22	36	0.13	0.35	46	N/A	N/A	N/A
5 y		0.17	0.24	23	0.21	0.32	25	0.24	0.57	39	N/A	N/A	N/A
10 y	Male:										0.841	2.22	44
	Both:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
	Female:										0.667	1.84	46
15 y	Male:	0.500	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.417	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.625	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.444	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

[a] See Annexe B (ICRP 1994) for data from which these reference values were derived.
[b] V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency.

Mo = month(s); N/A = not applicable; y =year(s)

Figure 2-6. Compartment Model to Represent Time-Dependent Particle Transport in the Respiratory Tract



Source: ICRP 1994

(See Table 2-6 for rates, half-lives, and fractions by compartment)

(Figure 2-5) and to reference values presented in Table 2-6. Table 2-6 provides clearance rates and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction per day and also as half-time. ICRP also developed modifying factors for some of the parameters, such as age, smoking and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

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

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

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

Table 2-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance Rates for Insoluble Particles				
Pathway	From	To	Rate (d^{-1})	Half-time[d]
$m_{1,4}$	AI_1	bb_1	0.02	35 d
$m_{2,4}$	AI_2	bb_1	0.001	700 d
$m_{3,4}$	AI_3	bb_1	0.0001	7000 d
$m_{3,10}$	AI_3	LN_{TH}	0.00002	—
$m_{4,7}$	bb_1	BB_1	2	8 h
$m_{5,7}$	bb_2	BB_1	0.03	23 d
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 d
$m_{7,11}$	BB_1	ET_2	10	100 min
$m_{8,11}$	BB_2	ET_2	0.03	23 d
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 d
$m_{11,15}$	ET_2	GI tract	100	10 min
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 d
$m_{14,16}$	ET_1	Environment	1	17 h

See next page for Part B

Table 2-6. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract (continued)

Part B

Partition of deposit in each region between compartments[b]		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

Source: ICRP 1994

[a] The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.

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

[c] It is assumed that the slow-cleared fraction f_s is size-dependent. For modeling purposes f_s is taken to be:

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

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

half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into 3 subcompartments to represent different clearance rates, all of which are slow.

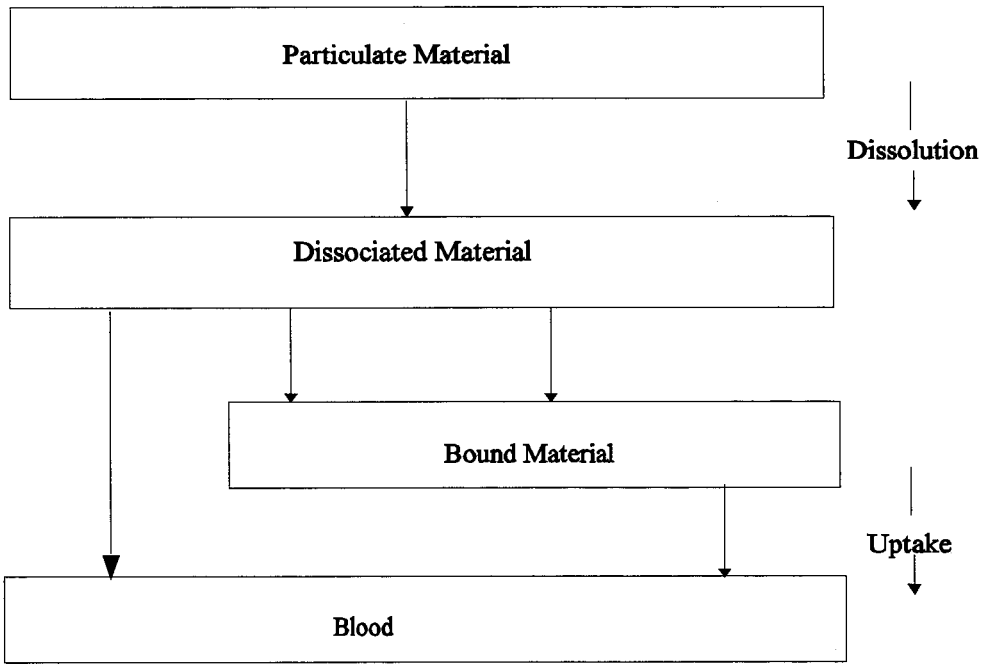
In the alveolar-interstitial region, human lung clearance has been measured. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time, and the remaining 70% are given a half-time of several hundred days. Over time, AI particle transport falls and some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

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. It is essentially a 2-stage process, as shown in Figure 2-7. First, there is a dissociation (dissolution) of particles; then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), and S (slow):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing. Type F uranium compounds include uranium hexafluoride, its mixture with uranyl fluoride, uranyl nitrate (which can behave as Type M), pure uranium trioxide, and uranium tetrafluoride (which can behave at Type M).

- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing. Type M compounds include unpure uranium trioxide, uranyl nitrate (which can behave as Type F), ammonium diuranate, uranium oxtaoxide (which can behave as Type S), and uranium tetrafluoride (which can behave as Type F).

Figure 2-7. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994

- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually. Type S compounds include uranium dioxide and uranium octaoxide (which can behave as Type M).

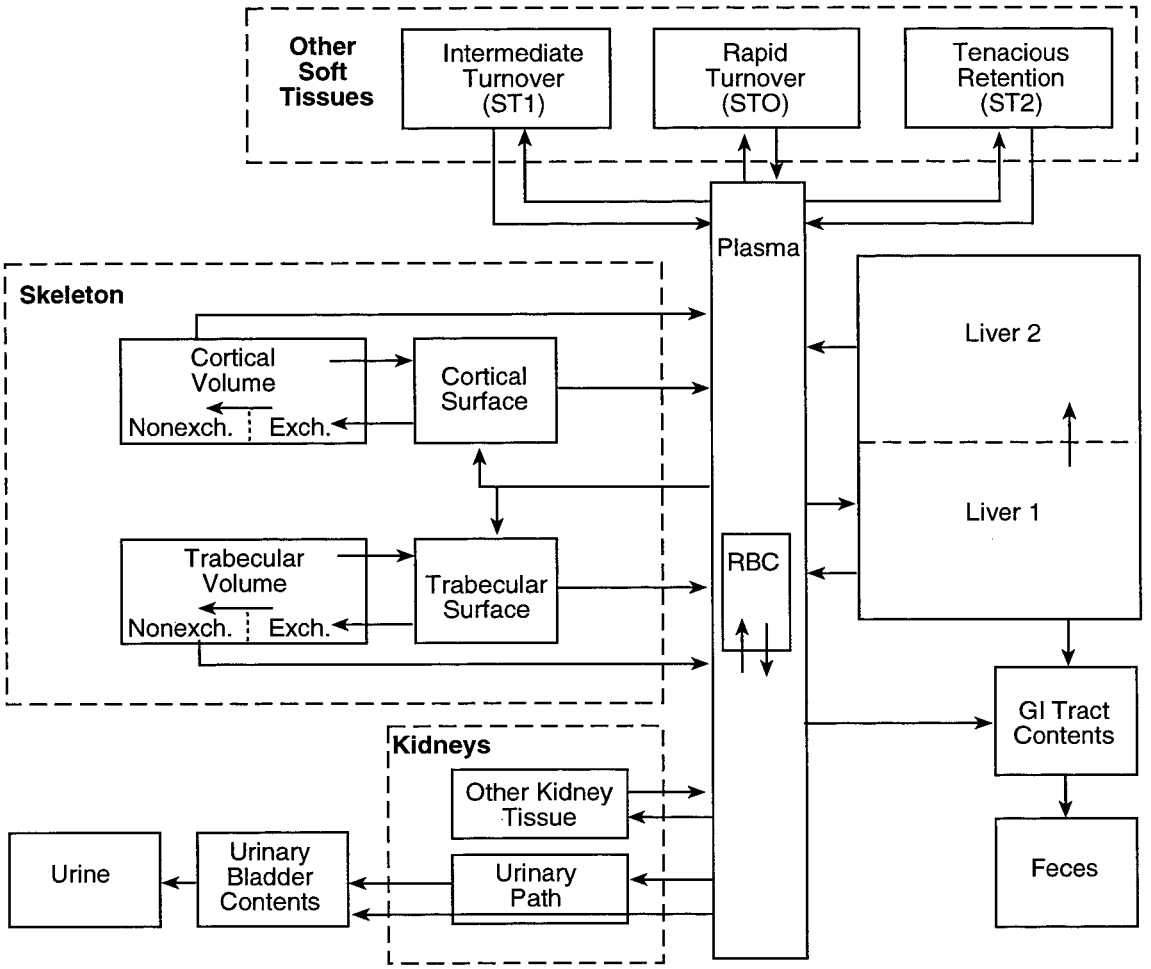
Biokinetic Model for Uranium (ICRP 1995). The ICRP biokinetic model for uranium is based on the generic model structure for alkaline earth elements described in *Publication 67* (ICRP 1993, as cited in ICRP 1995). Uranium (as the UO_2^{2+} ion) is similar to calcium (Ca^{2+}) with regard to skeletal kinetics. Some transfer rates in the biokinetic model for uranium are equated with bone formation rates. The early behavior of uranium in human circulation is represented reasonably well by treating plasma as a uniformly mixed pool, where uranium is removed at a rate of 35 d^{-1} (ICRP 1995) and where a soft tissue compartment (ST0) is in relatively rapid exchange with plasma (see Figure 2-8). Compartment ST0 is assumed to receive 30% of uranium leaving plasma and to have a removal half-time of 2 hours (from ST0 to plasma). ICRP assumed that 1% of uranium leaving the circulation (or 0.7% leaving plasma) deposits in red blood cells (ICRP 1995). The removal half-time from red blood cells to plasma is assumed to be 2 days.

Urinary excretion of uranium is assumed to arise from uranium moving directly from plasma to the urinary bladder contents. Approximately 60% of uranium leaves the blood directly to the bladder and another 12% is retained temporarily in the renal tubules before excretion. The liver is assumed to consist of two compartments, Liver 1 and Liver 2. The liver receives an estimated 1.5% of uranium leaving the blood, with over 90% returning to circulation.

Little direct information on the kinetics of uranium in children exists. Age-specific deposition of uranium in the skeleton is assumed to be proportional to the deposition of the alkaline earth elements. The rate of removal from deep bone is assumed to be the same as the age-specific bone turnover rate. Because children have higher amounts of uranium taken up by bone, deposition in soft tissues and excreta are likely lower in children than for adults.

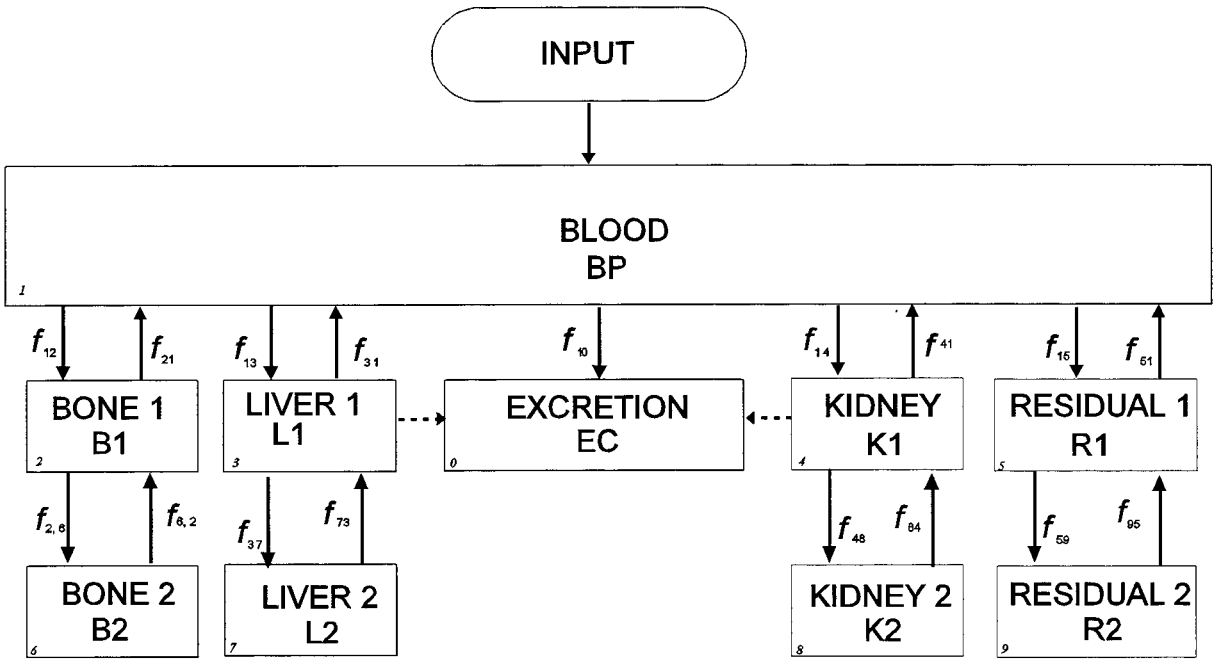
Sontag (1986) Pharmacokinetic Model. An extended multicompartmental model (see Figure 2-9) describing the kinetic behavior of uranium (absorption, distribution, and excretion as a function of time) in the organs of male and female rats was developed using data taken from experiments performed on 13-month-old male and female Sprague-Dawley rats intravenously injected with 1.54 mCi/kg (57 kBq/kg) ^{233}U-uranyl citrate and sacrificed at 7, 28, 84, 168, or 336 days after injection.

Figure 2-8. Biokinetic Model for Uranium after Uptake to Blood



Source: ICRP 1995

Figure 2-9. Multicompartmental Model



f = transfer coefficient (unitless)

Source: Sontag 1986

The model is composed of 10 compartments. These 10 compartments are connected by 17 linear transfer coefficients using 21 parameters. The whole system describes the flux of compounds between a central compartment (the blood) and outer compartments which connect with the central compartment only. The 10 compartments are labeled blood, bone 1, bone 2, liver 1, liver 2, kidney 1, kidney 2, residual 1, residual 2, and excretion. The organs are divided into two compartments; one compartment represents the short term and one represents the long term. For example, the short-term compartment for the bone is the bone surface and bone marrow, and the long-term compartment is the deep bone. In the liver, the short-term compartment is assumed to be the lysosomes, and the long-term compartment is assumed to be the telolysosomes. Separation of these organs into two components helps to account for the reabsorption and rapid excretion. Using the symbols BP=blood, EC=excretion, B1=bone 1, L1=liver 1, K1=kidney 1, R1=residual 1, B2=bone 2, L2=liver 2, K2=kidney, and R2=residual 2, the calculated transfer coefficients for this model are shown in Table 2-7.

Parallel evaluations produced 2 different values (ranges) for each of the 21 parameters. The maximum fractions of uranium in various compartments were as follows: bone, 0.0710 or 0.0735; liver, 0.0160 or 0.0146; kidney, 0.1777 or 0.4789; residual compartment, 0.0358 or 0.0481; and excretion compartment, 0.6995 or 0.3849 (if no back transfer to the blood compartment occurred). The time at which the maximum amount of the uranium in the organ is reduced to one-half is 0.0009 or 0.0013 days in the blood, 165 or 93 days in the bone, 6 or 7 days in the liver, 11 or 5 days in the kidney, and 5 or 6 days in the residual compartment. The cumulative radiation absorbed dose in the organ 365 days after injection of 56.6 kBq/kg body weight was 0.0002 or 0.0004 Gy to blood, 0.730 or 1.29 Gy to bone, 0.0268 or 0.0308 Gy to liver, 1.32 or 1.77 Gy to kidney, and 0.0061 or 0.0076 Gy to residual compartment. The ratio of single injection/continuous intake calculated for the same dose 1 year after the first injection was 0.018 or 0.003 to blood, 0.619 or 0.812 to bone, 0.422 or 0.355 to liver, 0.256 or 0.231 to kidney, 0.726 or 0.585 to residual compartment, and 1.024 or 1.023 to excretion compartment (Sontag 1986).

Fisher et al. (1991) Biokinetic Model A modified biokinetic model for uranium was developed for inhaled soluble uranium based on human data from an accidental release of uranium hexafluoride in Oklahoma. Urinary excretion data from 31 exposed workers were used to test two previously published compartmental models for inhalation exposure to uranium (ICRP 1979; Wrenn et al. 1989). Urinary uranium was measured periodically for 2 years following the accident. Statistical analysis showed that the Wrenn et al. (1989) model produced a better fit to the excretion data than the ICRP (1979) model.

Table 2-7. Sensitivity and Calculated Transfer Coefficients (d^{-1})

Transfer from-to	Symbol	Experimental value 1	Experimental value 2	Sensitivity
BP-EC	f_{10}	5.55E+2	2.09E+2	0.2
BP-B1	f_{12}	5.63E+1	3.99E+1	5.9
BP-L1	f_{13}	1.27E+1	7.94E0	3.3
BP-K1	f_{14}	1..41E+2	2.60E0	1.5
BP-R1	f_{15}	2.84E+1	2.61E+1	17.5
B1-BP	f_{21}	9.79E-3	1.84E-2	1.9
L1-BP	f_{31}	1.87E-1	2.70E-1	5.6
K1-BP	f_{41}	9.48E-2	3.65E-1	0.5
R1-BP	f_{51}	2.25E-1	3.41E-1	3.4
B1-B2	f_{26}	5.65E-3	6.49E-3	2.2
L1-L2	f_{37}	8.63E-3	9.40E-3	2.7
K1-K2	f_{48}	1.14E-3	1.22E-3	2.2
R1-R2	f_{59}	1.03E-2	8.60E-3	6.1
B2-B1	f_{62}	2.61E-3	4.43E-6	5.0
L2-L1	f_{73}	2.84E-3	3.49E-3	43.7
K2-K1	f_{84}	9.72E-4	1.22E-3	4.8
R2-R1	f_{95}	7.16E-4	1.38E-3	2.3
Varinz	V	6.63E-3	4.65E-3	–

– = Not applicable

Source: Sontag 1986

Parameters of the (Wrenn et al. 1989) model were then modified to further improve the fit to the workers excretion data. Changing the retention half-time in the kidney from 15 days to 6 days and the clearance half-time in the lung from 0.5 days to 0.03 days optimized the fit of the model to the experimental data. The model may be summarized with the following 5-term exponential equation:

$$y_u(t) = 1.5e^{-2.77t} + 0.028e^{-0.116t} + 0.0069e^{-0.0347t} + (4.8 \times 10^{-7}e^{-0.000462t}) + 3.2 \times 10^{-6}e^{-0.000139t}$$

where, $y_u(t)$ is fractional daily uranium excretion rate at t days after intake; the excretion constants in the 5 exponents corresponding to compartments with retention half-times of 0.25, 6, 20, 1,500, and 5,000 days.

The model was used to estimate uranium intakes; uranium burdens in the lungs, kidneys, and bones; and effective dose equivalent for each worker in the accident. Initial intakes of workers involved in the accident ranged from 470–24,000 µg uranium. The model estimated the maximum kidney concentrations in the workers as ranging from 0.048 to 2.5 µg U/g kidney tissue, renal toxicity was not observed in any of the workers (Fisher et al. 1990, 1991).

Based on this same data base, the NRC determined that the maximum uranium dose equivalent of workers on-site was 28 mrem (0.28 mSv). The maximum uranium dose equivalent of off-site individuals was 1.4 mrem (0.014 mSv). However, these radiological doses were small compared to the background radiation level of 106 mrem/year (1.06 mSv/year) in the area from which the data were collected (USNRC 1986).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

On the average, a given amount of an ingested uranium compound appears to be less toxic than the same amount of an inhaled uranium compound (Maynard and Hodge 1949; Stokinger et al. 1953). This finding may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only 0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract (Harrison

and Strather 1981; Hursh et al. 1969; ICRP 1979; Larsen et al. 1984; LaTouche et al. 1987; Leggett and Harrison 1995; Maynard et al. 1953; Sullivan 1980a; Wrenn et al. 1985, 1988b). The ICRP (1995) recommends a gastrointestinal absorption reference fraction of 0.02 for uranium ingested in relatively soluble form and 0.002 for insoluble compounds. On the basis of the toxicity of different uranium salts in animals, it was concluded that the relatively more soluble salts (uranyl nitrate hexahydrate, uranyl fluoride, uranium tetrachloride, uranium pentachloride) were most toxic, the slightly soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) were of intermediate toxicity, and the insoluble compounds (uranium tetrafluoride, uranium dioxide, uranium tetrachloride, triuranium octaoxide) were nontoxic (Orcutt 1949).

In inhalation exposures, uranium compounds are usually inhalable aerosols. Thus, particle size plays a vital role in tissue dose. Particles larger than 5 μm AMAD are likely to be transported out of the tracheobronchial region by mucocilliary action and swallowed into the gastrointestinal tract, where absorption is minimal (ICRP 1979). The less soluble compounds (uranium trioxide, uranium tetrafluoride), designated Type M by the ICRP (1995), are more likely to remain in the lung tissue and associated lymph glands for weeks. The relatively insoluble compounds (uranium dioxide, triuranium octaoxide), designated Type S by the (ICRP 1995), are likely to remain in the lungs for years (Eidson 1994). This retention of uranium in the lung can lead to a significant pulmonary radiation dose.

In addition, the sequestration patterns of the different uranium compounds are important determinants for the target organ chemical and radiological toxicities of these compounds. The site of deposition for the soluble uranium compounds (uranyl nitrate, uranium tetrachloride, uranium hexafluoride) is the bone, while the insoluble compounds (uranium hexafluoride, uranium dioxide) accumulate in the lungs and lymph nodes (Stokinger 1953).

2.4.2 Mechanisms of Toxicity

The dual modes of uranium chemical and radiological toxicity are not usually separately identifiable by end point. The renal and respiratory effects from exposure of humans and animals to uranium are usually attributed to the chemical properties of uranium, while the theoretically potential excess cancers are usually attributed to the radiation properties of this substance. Although the net effects on the lungs and kidneys have been suggested to be a cooperative action of the chemical and radiation properties, with a

complementary mechanism of action, this relationship has not been demonstrated experimentally (Ballou et al. 1986; Dockery et al. 1993; Dungworth 1989; Filippova et al. 1978; Leach et al. 1984; Spiegl 1949; Spoor and Hursh 1973; Stokinger et al. 1953). UNSCEAR has considered that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a radiological toxicity, which has not been observed in either humans or animals (UNSCEAR 1993; Wrenn et al. 1985).

The most sensitive indicator of uranium toxicity to mammals, and perhaps humans, is nephrotoxicity. While acute high level exposure to uranium compounds can clearly cause nephrotoxicity in humans (Pavlaikis et al. 1996; Zhao and Zhao 1990), the evidence for similar toxicity as the result of long-term lower level occupational exposures is equivocal. Epidemiologic studies have not noted an increase in deaths from urogenital or renal diseases (Brown and Bloom 1987; Checkoway et al. 1988; Dupree et al. 1987; Lundin et al. 1969; Polednak and Frome 1981), and follow-up studies have failed to identify significant damage to human kidneys following occupational exposure to uranium (Eisenbud and Quigley 1955; Hursh and Spoor 1973; Luessenhop et al. 1958), for which regulatory limits are set to prevent damage. A recent comparison of autopsy kidney tissue samples revealed no differences between 7 uranium workers and 6 referents with no known exposure to uranium (Russell et al. 1996). One epidemiologic study provided evidence of nephrotoxicity following occupational exposure to uranium. Nephrotoxicity, indicated by β_2-microglobulinuria and aminoaciduria due to decreased tubular reabsorption, was reported in a group of 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the occupational standard of 3.7 Bq/m^3 (currently 5 Bq/m^3 [0.2 mg/m^3]) by #8-fold. Cement workers were used as controls in this study (Thun et al. 1985).

Many animal studies have shown that inhalation, oral, or dermal exposure to uranium results in kidney damage. The damage was histologically manifested as glomerular and tubular wall degeneration. Ultrastructural analysis showed damage to the endothelial cells in the glomerulus, such as loss of cell processes, and reduction in the density of the endothelial fenestrae (Avasthi et al. 1980; Haley 1982; Haley et al. 1982; Kobayashi et al. 1984). In the terminal segments of the proximal convoluted tubules, there was a loss of the brush border, cellular vacuolization, and necrosis. Tubular reabsorption of solutes was disrupted. Functionally, this process led to a disruption of the tubular solute reabsorption and to a decrease in the filtration rate of the glomerulus, as assessed by creatinine or inulin clearance or by proteinuria (Bentley et al. 1985; Blantz 1975; Leach et al. 1973; Morrow et al. 1982). Excessive urinary excretion of protein,

glucose, enzymes, or amino acids such as catalase or alkaline phosphatase are additional indicators of uranium-induced renal pathology (Maynard et al. 1953) by inhalation exposure (Bentley et al. 1985; Diamond et al. 1989; Haley et al. 1982; Leach et al. 1984; Maynard et al. 1953; Morrow et al. 1982).

A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. Uranium is usually combined with either bicarbonate or a plasma protein in the blood. In the kidneys, uranium is released from bicarbonate and is free to combine to form complexes with phosphate ligands and proteins in the tubular wall to cause damage. Uranium is not tightly bound and is released again within a few days. Within a week following exposure, uranium is largely cleared from the kidneys, and the tubules begin to regenerate. Although the regenerated epithelium has histological differences from its normal state, it is often difficult to detect histological signs of kidney damage a month after exposure because all remaining functional damage is subtle. An alternative mechanism through which uranium exerts its renal toxicity has been suggested by the results of a study conducted with rabbit kidney cells *in vitro*. In this study, uranyl nitrate hexahydrate inhibited both sodium transport-dependent and independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule. Ouabain-insensitive adenosine triphosphatase (ATPase) activity exhibited the greatest sensitivity to uranyl nitrate hexahydrate and was significantly inhibited at submillimolar concentrations (Brady et al. 1989). Perhaps both of these activities combine to cause renal damage. In addition, because uranium is a predominantly alpha-emitting radionuclide, current theories on cellular necrosis by high-LET alpha radiation imply a contributory role to the cellular degenerative nephrotoxic changes (BEIR 1980, 1988, 1990; Filippova et al. 1978; Sanders 1986; UNSCEAR 1982, 1986, 1988).

Most studies of respiratory diseases reported for uranium involve noncancerous alveolar epithelium damage in type II cells. These changes are characterized by interstitial inflammation of the alveolar epithelium leading eventually to emphysema or pulmonary fibrosis in acute exposures or to hyperplasia, hypertrophy, and transdifferentiation (metaplasia) in chronic exposures (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992). However, the lack of significant pulmonary injury in most inhalation animal studies indicates that other potentially toxic contaminants such as inhalable dust particles, radium, or radon may contribute to these effects.

Large doses of ionizing radiation have the actual or theoretical potential of being carcinogenic, teratogenic, and mutagenic. Since uranium has a low specific activity but emits high LET alpha particles

that are densely ionizing along their track length, studies have been conducted to determine if uranium can produce these effects in humans and animals. The 4 to 8 MeV alpha particles from uranium travel through 40–70 μm in soft tissue, incrementally transferring their kinetic energy to the series of atoms and molecules with which they interact along their short, straight paths. Consequently, only structures within this range from the site of the deposition of uranium may be affected. If a DNA molecule is intersected and damaged without resulting in cell death, a range of theoretical effects can result. DNA has been found to be the most radiosensitive biological molecule, and ionizing radiation has been observed to damage individual chromosomes. The main result from low level ionizing radiation exposure is DNA damage or fragmentation. Viable cells repair the damage, but repair errors can result which produce gene mutations or chromosomal aberrations. Such events may result in such highly rare events as carcinogenesis or teratogenesis, but there is currently no evidence for radiation mutagenesis in humans. Chromosomal aberrations following large radiation doses have been demonstrated in humans and in research animals, showing that ionizing radiation can both initiate and promote carcinogenesis, and interfere with reproduction and development. Cancer is a well-known effect of ionizing radiation exposure, but it has never been associated with exposure to uranium. Likewise, no genetic changes due to radiation have ever been observed in any human population exposed at any dose (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988). For these reasons, UNSCEAR has stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either humans or animals (Wrenn et al. 1985). The EPA also used chemical toxicity as the basis for their 20 μg/L interim drinking water limit for uranium published in 1991 (currently withdrawn).

2.4.3 Animal-to-Human Extrapolations

Kidney damage and respiratory disease are the most significant health effects in animals from the metallotoxicity of uranium. Because the biological systems through which these effects are mediated are common to both animals and humans (Brady et al. 1989; Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992), it is reasonable that animals are appropriate surrogates for humans in this regard. This assumption is consistent with evidence in humans for respiratory (Kathren and Moore 1986, Waxweiler et al. 1981a) and renal (Bernard and Struxness 1957; Fisher et al. 1991; Kathren and Moore 1986; Luessenhop et al. 1958; Thun et al. 1985; USNRC 1986; Waxweiler et al. 1981a; Zhao and Zhao

1990) effects. The data from these studies support the assumption of biological similarity in the renal toxicity of uranium in animals and humans. Nevertheless, a considerable uncertainty is associated with animal-to-human extrapolation regarding the renal toxicity of uranium exposure because the renal toxicity of animals varies with species.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Uranium is an alpha-emitting, radioactive, heavy metal that occurs naturally in the earth's crust at an average concentration of about 2 ppm (approximately 1 pCi/g). Uranium exists in several isotopic forms. The most toxicologically important forms are anthropogenic ^{232}U and ^{233}U and naturally occurring ^{234}U, ^{235}U, and ^{238}U. Uranium isotopes decay by alpha emission. ^{238}U decays through 16 radioactive progeny, including ^{234}U, to reach stable lead-206 (^{206}Pb), while ^{235}U decays through 13 radioactive progeny to reach stable ^{207}Pb. This profile discusses the chemical and radiological health effects of isotopes of uranium (natural, enriched, and depleted) and the various compounds in which uranium is usually found. The health effects of daughter isotopes (radium and radon) are addressed in other toxicological profiles (consult the ATSDR toxicological profiles for radium and radon for more information regarding these radionuclides).

Naturally occurring uranium is an isotopic mixture containing a large percentage of ^{238}U and very small percentages of ^{234}U and ^{235}U, by mass. The industrial process called enrichment is used to increase the percentage of ^{235}U and decrease the percentage of ^{238}U in natural uranium. This results in a continuum of additional isotope mixtures in which the percentage of ^{235}U is either larger (enriched uranium) or smaller (depleted uranium) than that of natural uranium. Natural uranium consists of 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U by weight and has a very low specific activity (0.68 μCi/g). Uranium enrichment for commercial nuclear energy produces uranium that contains about 3% ^{235}U; this is called 3% enriched uranium. Uranium enrichment for other purposes, including nuclear weapons production, can produce uranium containing as much as 97.3% ^{235}U and having a higher specific activity (. 50 μCi/g). Depleted uranium is the byproduct of the enrichment process. Depleted uranium has even less specific activity (0.33 μCi/g) than natural uranium.

Uranium is present in the body at very low or trace concentrations and is not known to be an essential element. Human intakes are constant through very small amounts of natural uranium in food and water, and even smaller amounts in air. The following anthropogenic activities increase the potential for human exposure to uranium: mining, milling, and handling uranium; processing uranium ore end products (uranium dioxide, uranium hexafluoride); producing nuclear energy and nuclear weapons; producing phosphate fertilizers from phosphate rocks that contain much higher-than-average levels of uranium; and improperly disposing of wastes. Occupational exposure to airborne uranium ore dust occurs in uranium mines and mills and in processing plants. Typically, uranium represents only 0.2–5% by weight of the ore.

The deposition of inhaled dust particles in the lungs depends on the particle size and the absorption depends on the solubility of the compound. Very small particles, on the order of 1 μm AMAD, are deposited in the alveolar region or deep lung spaces. As particle size increases above 2–3 μm AMAD, there is an increasing likelihood of deposition in the tracheobronchial region. Dust particles that have deposited are rapidly transported out of the tracheobronchial region by mucociliary action and swallowed. The more soluble compounds are more likely to be absorbed into the blood at the alveolar level within days. Ingested uranium that has been cleared from the lungs by mucocilliary action and swallowed is only partly absorbed into the blood. This is true even for the more common soluble salts (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate). Uranium is usually found in compounds that can break down and recomplex to form other compounds. In body fluids, tetravalent uranium is likely to oxidize to the hexavalent form, followed by formation of the uranyl ion. Uranium generally complexes with citrate, bicarbonates, or protein in plasma.

According to the ICRP (1995), the more soluble compounds (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) are more likely to be absorbed into the blood from the alveoli within days and are assigned to inhalation Type F (fast dissolution). The less soluble compounds (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide) are more likely to remain in the lung tissue and associated lymph glands for weeks and are designated Type M (medium dissolution). The relatively insoluble compounds (uranium dioxide, triuranium octaoxide) may remain in the lungs for years and are designated Type S (slow dissolution). The ICRP (1995) recommends the following absorption factors for humans for inhaled compounds that subsequently enter the gastrointestinal tract: 2% for soluble compounds and 0.2% for less soluble compounds.

The main site of long-term retention for soluble uranium compounds (uranyl nitrate, uranium tetrachloride, uranium dioxide) is the bone, while the inhaled insoluble compounds (uranium tetrafluoride, uranium dioxide) that are deposited in the deep respiratory tract tend to accumulate in the lungs and pulmonary lymph nodes.

Ingested uranium is excreted mostly in the feces; urinary excretion is generally low. The biological half-times of soluble uranium compounds (uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate) are estimated in days or weeks; those of the less soluble compounds (uranium tetrafluoride, uranium dioxide, triuranium octaoxide) are estimated in years. No information is currently available on the excretion of dermally absorbed uranium. Transdermally absorbed uranium is expected to behave identically to uranium compounds absorbed through the lungs and the gastrointestinal tract.

Because the specific activities of natural and depleted uranium are low, no remarkable noncancerous radiological health hazard is expected (and none has been observed) from exposure to natural and depleted uranium. The results of the available studies in humans and animals are consistent with this conclusion. According to the BEIR IV report, if uranium's radiation were carcinogenic in humans, the most likely carcinogenic effect in humans would be bone sarcoma. However, even highly-enriched uranium has not been found to produce cancer, including that of the bone, in exposed humans. Evidence from animal studies suggests adverse effects reported from such exposures include damage to the epithelium of the lungs (fibrosis) and cardiovascular abnormalities (friable vessels).

The chemical action of all isotopes and isotopic mixtures of uranium are identical, regardless of the specific activity, because chemical action depends only on chemical properties. Thus, the chemical toxicities of natural, depleted, and enriched uranium are identical. Current evidence from animals studies suggests that the toxicity of uranium is mainly due to its chemical damage to kidney tubular cells, leading to nephritis.

Evidence also suggests that the toxicity of uranium varies according to the route of exposure and to its compounds. This finding may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds. Only <0.1–6% of even the more soluble uranium compounds are absorbed in the gastrointestinal tract. On the basis of the toxicity of different uranium salts in animals, it was concluded that the relatively more water-soluble salts (uranyl nitrate hexahydrate, uranyl fluoride, uranium pentachloride) were primarily renal and systemic toxicants. The less water-soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) were of moderate-to-low toxicity, while the insoluble

compounds (uranium tetrafluoride, uranium dioxide, uranium peroxide, triuranium octaoxide) were primarily pulmonary toxicants. Generally, hexavalent uranium, which forms soluble compounds, is more likely to be a systemic toxicant than the less soluble tetravalent uranium. The available data on both the more important soluble and insoluble uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity in humans. This low toxicity results from the high exposures to which animals in these studies were exposed, without adverse effects in some cases. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce very severe, perhaps fatal, injury to animals at the levels of human exposures to uranium reported in the literature.

Particle size determines the point of deposition site of pulmonary-inhaled aerosols. The pulmonary deposition site is an important factor in determining the toxicity of an aerosol. Small particles (#2 μm AMAD) are deposited in the deep respiratory tract. Larger particles are deposited in the tracheobronchial region, where they are transported by mucociliary action to the throat and swallowed into the gastrointestinal tract where absorption is minimal. The less soluble compounds are more likely to remain in the lung tissue and associated lymph glands either for weeks (uranium trioxide, uranium tetrafluoride) or for years (uranium dioxide, triuranium octaoxide), resulting in significant pulmonary retention in inhalation-exposure toxicity and a greater dose of alpha radiation. Long-term retention of inhaled particles of insoluble compounds can cause pulmonary ailments.

The kidneys have been identified as the most sensitive target of uranium toxicosis, consistent with the metallotoxic action of a heavy metal ion, such as the uranyl ion, but epidemiological studies indicate that exposure to air concentrations within current occupational limits may not produce renal effects. The toxic action of uranium is mediated by accumulation of uranium in the renal tubular epithelium to induce cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubules in humans and animals. Heavy metal ions are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis. However, epidemiologic studies have not provided evidence of uranium's nephrotoxicity or urogenital toxicity in humans. One study found mild nephrotoxicity, indicated by β_2-microglobulinuria and aminoaciduria due to decreased tubular reabsorption, in 39 male uranium mill workers exposed for more than a year to uranium concentrations exceeding the occupational standard of 1.0×10^{-10} μCi/mL (3.7 Bq/m^3 or 0.15 mg/m^3) by up to 8-fold. Nephritis with edema (including nephrosis) was identified as the cause of death of 11% of a cohort of

uranium miners exposed to uranium dust (and radon daughters for an average of 821 WLM). However, the incidence was actually lower than the national average using Standard Mortality Ratio (SMR) analysis. The nephrotoxic effects of uranium in humans may include damage to the glomerulus as evidenced by histopathological changes in the kidneys of former uranium mill workers. However, the negative findings regarding renal injury among current uranium miners and mill workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure.

In animal studies, observations in acute- and intermediate-duration exposures to uranium compounds provide evidence that uranium is nephrotoxic in high doses. Histopathological examination of the kidneys of these animals following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, lesions, and decreased glomerular filtration rates. The damage in animals is histologically manifested as glomerular and tubular wall pathology. A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. An alternative mechanism involving the inhibition of both sodium transport-dependent and independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule has also been proposed.

Respiratory diseases have been associated with human exposure to uranium dust, and several epidemiologic studies of uranium miners, millers, and processors are considered in this profile. Respiratory disease in uranium miners has been linked to exposure to uranium-containing dust. In several of these studies, the investigators concluded that although uranium mining clearly elevates the risk for nonmalignant respiratory disease, the etiology of the excess risk is not clearly identifiable because of concurrent exposure to known potent respiratory tract toxicants (including inhalable dust particles, silica, nickel oxide, cobalt oxide, radon daughters, and vanadium pentaoxide). Several animal studies involving uranium-containing dusts, such as carnotite mineral dust, reported serious respiratory effects. However, animals exposed to very high doses of dust-free uranium (as uranyl nitrate hexahydrate, uranium tetrachloride, uranium dioxide, uranium trioxide, uranium tetraoxide, uranyl fluoride, uranium tetrafluoride, or uranium acetate) through the inhalation or oral route in acute-, intermediate-, or chronic-duration exposures failed to develop these respiratory ailments. The lack of significant pulmonary injury in oral animal studies indicates that other factors such as diverse inorganic inhalable dust particles, radium, or radon progeny may contribute to these effects. In studies in which humans and animals inhaled uranium hexafluoride, the associated hydrofluoric acid could have been responsible for or could

have aggravated the observed respiratory effects because uranium hexafluoride is hydrolyzed on contact with water to uranyl fluoride and hydrogen fluoride, the latter of which solubilizes into hydrofluoric acid. Acute overexposures to hydrogen fluoride and hydrofluoric acid can lead to death from respiratory failure or cardiac arrythmia.

Uranium has not been implicated in the production of human lung cancer. Since uranium is weakly radioactive, it has been assumed to be potentially carcinogenic at occupational levels by NIOSH. EPA had classified uranium similarly, but has since withdrawn this classification for review. IARC has no classification for uranium. Studies do not indicate any level of uranium carcinogenicity. No significant difference in cancer (of the lungs) was found between workers occupationally exposed to uranium and control populations. Other detailed studies conducted between 1950 and 1967 on the association between uranium mining and an increased incidence of cancer found lung cancer in the miners over 6 times the rate expected. However, the miners were concurrently exposed to other known or potential cancer-causing substances such as radon and its progeny, tobacco smoke, phosgene gas, mercury, and solvents (carbon tetrachloride and trichloroethylene). Radon progeny in the mines, and not the uranium, were clearly identified as the carcinogenic agents. (For further information on cancer risks from radon, refer to the ATSDR *Toxicological Profile for Radon* [ATSDR 1990c]). Uranium also appears to be noncarcinogenic in animals. Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels.

Minimal Risk Levels (MRLs) have been derived for the effects from inhalation and oral exposure to uranium, and those values are identified in this section and their bases are detailed in Appendix A. MRLs for radiological exposure were not calculated because:

- no data are available for use in calculating radiological MRLs for any duration because no radiological effects were identified in any of the available studies that used natural uranium as a test material;
- the MRLs for chemical effects would adequately protect against the possible radiotoxicity of natural and depleted uranium because radiological effects are not expected to occur, based on the low specific activities of these isotopic mixtures and the current toxicity data in humans and animals;
- the studies that reported potential radiological effects (severe pulmonary fibrosis, friable blood vessels) used highly enriched uranium in a single inhalation exposure (Filippova et al. 1978; Morris et al. 1989);

- UNSCEAR has considered that limits for natural (and depleted) uranium in food and drinking water (the most important sources of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity, which has not been observed in either humans or animals (UNSCEAR 1993; Wrenn et al. 1985).

Lack of radiological effects (see Tables 2-1, 2-2, 2-3, and 2-4) in studies that used natural uranium is due to the low specific activities of natural and depleted uranium, which are 0.67 and 0.3 μCi/g, respectively. In comparison, the calculated specific activity for 97.5% enriched uranium is approximately 50 μCi/g.

Table 2-8 shows the mass equivalents for natural and depleted uranium for radiation levels that caused potential radiological effects in rats exposed once for 100 minutes to airborne 92.8% enriched uranium with an estimated specific activity of 51.6 μCi/g (Morris et al. 1989). These mass equivalent values for natural and depleted uranium for the minimal concentration of radioactivity that is expected to induce potential radiological effects are well above levels that would be expected to be inhaled or ingested. In addition, the mass equivalents for natural and depleted uranium for potential radiological effects are 3,600 and 76,500 times higher, respectively, than the occupational exposure limits (short-term exposure) recommended by the National Institute for Occupational Safety and Health (NIOSH 1997). Therefore, MRLs for uranium based on studies that used enriched uranium are inappropriate.

Chemically, natural and depleted uranium are identical. Therefore, the MRLs calculated for chemical effects, based on studies that tested natural uranium, are applicable to the chemical actions of depleted uranium because the nature and extent of chemical toxicity are determined only by chemical properties.

All of the MRLs derived for uranium are based on renal effects, the most sensitive toxic end point. Uranium has been identified as a nephrotoxin, exerting its toxic effect by chemical action in the proximal tubules in humans and animals, with nephron involvement expected at higher doses. Some acute high-level exposures have resulted in renal effects in humans (Pavlaikis et al. 1996; Zhao and Zhao 1990), while others have not (Eisenbud and Quigley 1955; Fisher et al. 1990). A study of the kidney functions of past uranium mill workers chronically exposed to uranium revealed renal tubular dysfunction, as manifested by mild proteinuria; aminoaciduria; and a correlation between the excretion of β_2-microglobulin (relative to that of creatinine), and the length of time that the uranium workers had spent in the yellowcake (uranium dioxide) drying and packaging area, the work area with the highest exposures to insoluble uranium (Thun et al. 1985). Glomerular function was unaffected by uranium exposure. A number of epidemiological studies have demonstrated no relation between occupational exposure to

Table 2-8. Enriched, Natural, and Depleted Uranium Mass Equivalents for Radiological Effects

Intake duration	Effect	Highly eniched uranium radioactivity concentration[a]	Natural uranium mass equivalent[b]	Depleted uranium mass equivalent[c]	Threshold Limit Value[d]
Acute	Severe alveolar fibrosis	5 μCi/m^3 (= 0.111 g/m^3)	7.2 g/m^3	15.3 g/m^3	0.0002 g/m^3
Intermediate	No data[e]	No data	No data	No data	N/A
Chronic	No data	No data	No data	No data	N/A

[a] Value calculated from a highly ^{235}U-enriched uranium dioxide exposure of 111 mg/m^3 (97.8 mg uranium/m^3) and a specific activity of 1.91 kBq/g (51.6 μCi/g) (Morris et al. 1990)

[b] Value based on a highly ^{235}U-enriched dioxide radioactivity concentration of 5 μCi/m^3 and a specific activity of 0.7 μCi/g for natural uranium

[c] Value based on a highly ^{235}U-enriched dioxide radioactivity concentration of 5 μCi/m^3 and a specific activity of 0.33 μCi/g for depleted uranium

[d] This is a time-weighted average (TWA) concentration for short-term (8-hour) inhalation exposure to insoluble natural uranium compounds in the workplace for which no adverse effects (chemical or radiological) are expected (NIOSH 1994)

[e] Because the observations in the Morris et al. (1989) studies were made through 720 days, its conclusions may be applicable to intermediate and chronic durations

uranium and deaths from renal disease (Brown and Bloom 1987; Checkoway et al. 1988; Dupree et al. 1987; Lundin et al. 1969; Polednak and Frome 1981). The evidence is clear that exposure to uranium can cause renal effects in humans under certain conditions, threshold levels of exposure at which these effects occur have been reported over the range of 0.2 to 3 μg U/g of kidney; however, human organ concentrations are not typically measurable because of the invasive methods that are required. An extensive animal toxicity database, particularly for the inhalation route, indicates that renal effects are also the most sensitive toxic end point in several mammalian species. The effects were dose-dependent and ranged from minimal microscopic lesions in the tubular epithelium and increased urinary catalase (for low doses) to severe necrosis of the tubular epithelium (for high doses) (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953).

The effects of uranium in animal experiments were also compound-dependent, the more water-soluble compounds (e.g., uranyl nitrate) causing much greater renal toxicity than insoluble compounds (e.g., uranium dioxide) when the dose contained equivalent amounts of uranium. ATSDR has determined that the toxicity database for uranium justifies the derivation of separate MRLs for soluble and insoluble forms of uranium for certain durations and routes of exposure. This is based on toxicokinetic evidence that absorption of uranium (and concentration in target tissue) is significantly greater during exposure to the more water-soluble compounds. Soluble forms include uranyl fluoride, uranium tetrachloride and uranyl nitrate hexahydrate; insoluble forms include uranium tetrafluoride, uranium dioxide, uranium trioxide, and triuranium octaoxide. Where the database is not extensive enough to allow separate MRLs, the MRL for the soluble form should be protective for health effects due to all forms of uranium.

Inhalation MRLs.

No acute-duration inhalation MRLs were developed for uranium because of the lack of suitable data.

- An MRL of $8x10^{-3}$ mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to insoluble compounds of uranium.

This MRL is expected to be protective for soluble uranium compounds by an order of magnitude. The MRL is based on a study in which a NOAEL of 1.1 mg U/m^3 was observed for renal effects in dogs and adjusted for intermittent exposure (6 hours/day, 6 days/week) and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). Dogs were exposed to uranium

dioxide dust at concentrations of 1.1 mg U/m^3, 8.2 mg U/m^3, or 9.2 mg U/m^3 for 5 weeks, 6 days/week, 6 hours/day (Rothstein 1949b). Mortality, body weight changes, standard hematology (except in the 8.2-mg U/m^3 group), blood and urine chemistries, pathology, and uranium distribution in tissues were measured. No dogs died from exposure to uranium dioxide dust. Additionally, no significant weight changes, or biochemical changes in blood or urine were seen at any concentration. No hematological changes were attributable to uranium dioxide dust. Histopathological changes in the kidney were not observed in any group except for "very slight" renal tubular degeneration in 2 of 6 dogs at 8.2 mg U/m^3. A NOAEL of 1.1 mg/m^3 was identified for the study. For further details, see Appendix A.

- An MRL of $4x10^{-4}$ mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to soluble compounds of uranium.

The intermediate-duration inhalation MRL for soluble forms of uranium is based on a study that observed a LOAEL of 0.15 mg U/m^3 for renal effects in dogs (Rothstein 1949a). The LOAEL was adjusted for intermittent exposure (6 hours/day, 6 days/week) and multiplied by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability). In this study, dogs were bodily exposed to 0.15, 2.2, or 9.2 mg U/m^3 of uranyl fluoride dust for 6 hours/day, 6 days/week for 5 weeks (Rothstein 1949a). Clinical signs of toxicity, mortality, body weight changes, hematology, and blood and urine chemistries were monitored; selected organs were histopathologically examined and uranium levels determined. Severe toxicity was observed at the highest concentration (9.2 mg U/m^3) leading to death. The two animals in this group showed signs of anorexia, rhinitis, and polydipsia. Histopathological examination of the kidney revealed "severe" tubular lesions. Dogs exposed to 0.15 or 2.2 mg U/m^3 had no clinical signs of toxicity or significant weight changes. At 0.15 mg U/m^3, blood NPN and urinary amino acid nitrogen were normal in three dogs, while one of the three had increased urinary protein (not all tests were run on all dogs). Histopathological examination of the kidneys revealed "moderate" damage at 2.2 mg U/m^3 and "slight" changes in 50% of the dogs at 0.15 mg U/m^3. A LOAEL of 0.15 mg/m^3 for minimal microscopic lesions in the renal tubules was identified for this study. For further details, see Appendix A.

- An MRL of $3x10^{-4}$ mg U/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to soluble compounds of uranium.

The chronic-duration inhalation MRL for soluble forms of uranium is based on a NOAEL of 0.05 mg U/m^3 for renal effects in dogs exposed to uranium tetrachloride (Stokinger et al. 1953). The NOAEL was adjusted for intermittent exposure (6 hours/day, 5.5 days/week) and multiplied by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability). In this study, dogs of both sexes were exposed via inhalation to uranium tetrachloride for 6 hours a day, Monday–Friday, and 3 hours on Saturday (5.5 days a week) for 1 year at concentrations of 0, 0.05, and 0.2 mg U/m^3. The animals were monitored for body weight alterations, clinical signs of toxicity, and biochemical alterations in the blood and urine. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined. Histological and biochemical examinations revealed a NOAEL of 0.05 mg U/m^3 and minimal microscopic lesions in the renal tubules in the 0.2 mg U/m^3 dose level dogs. For further details, see Appendix A.

Oral MRLs.

No acute- or chronic-duration oral MRLs could be developed for uranium because of a lack of suitable data.

- An MRL of $2x10^{-3}$ mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to soluble compounds of uranium.

The intermediate-duration oral exposure MRL was derived from a LOAEL of 0.05 mg U/kg/day observed for renal effects in New Zealand rabbits receiving uranium as uranyl acetate in drinking water for 91 days (Gilman et al. 1998b). The LOAEL was adjusted by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability). Time-weighted average (TWA) (as mg U/kg/day) calculated by the authors from fluid intake data were: males: 0, 0.05, 0.20, 0.88, 4.82, and 28.70 mg U/kg/day; females: 0, 0.49, 1.32, and 43.02 mg U/kg/day. Urinalysis was performed at 30, 60, and 91 days and dye clearance tests were performed 1 week prior to termination, using standard bromsulfophthalein (BSP) and phenolsulfonphthalein (PSP) test procedures for liver and kidney function, respectively. After 91 days, animals were sacrificed, hematological parameters and serum chemistry were analyzed, and histopathological examination was performed on 27 tissues from each animal. No significant exposure-related differences in weight gain, food consumption, water intake, hematological, or biochemical parameters were noted. Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in males. For further information, see Appendix A.

It is likely that the MRL level for intermediate-duration oral exposure would also be protective for chronic-duration oral exposure. This is because the renal effects of uranium exposure are more dependent on the dose than on the duration of the exposure. Data from a large number of animal studies indicate that renal damage caused by threshold and sublethal doses was overcome and obscured by regeneration of the tubular epithelium, especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a, 1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949c, 1949d; Russell 1996; Spiegl 1949; Stokinger et al. 1953). Such repair, once completed, is histologically indistinguishable from undamaged kidney tissue.

Death. The lethal effects of exposure to uranium compounds have been investigated in humans and animals. Data from these studies indicate that uranium compounds have a low order of mammalian toxicity by the inhalation, oral, and dermal routes. No deaths are causally associated with prolonged occupational exposure to inhaled uranium compounds (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Gottlieb and Husen 1982; Hadjimichael et al. 1983; Lundin et al. 1969; Polednak and Frome 1981; Samet et al. 1984, 1986; Scott et al. 1972; Waxweiler et al. 1983). Although accidental inhalation exposure to a high concentration of uranium hexafluoride has resulted in human fatalities, those deaths were not associated with uranium (Kathren and Moore 1986; Moore and Kathren 1985; USNRC 1986). These accidents resulted in the generation of concentrated aerosols of uranyl fluoride and highly toxic hydrofluoric acid. In all cases, deaths were attributed to injury to the respiratory tract associated with inhalation of hydrofluoric acid. No deaths have been reported in humans from oral or dermal exposure to uranium compounds. Uranium compounds have caused death in experimental animals by the inhalation, oral and dermal routes. Death was attributed to renal failure. However, the levels of uranium necessary to cause fatalities in experimental animals are far (>1,000 fold) above any plausible human exposure either in the workplace or at hazardous waste sites (Leach et al. 1984; Spiegel 1949; Maynard and Hodge 1949; Orcutt 1949). On the basis of the available data, exposure to environmental uranium or to uranium at levels found at hazardous waste sites will not be lethal to humans.

Systemic Effects.

Respiratory Effects. General damage to pulmonary structures, usually noncancerous alveolar epithelium damage of type II cells, can occur upon inhalation of insoluble reactive chemicals such as some uranium compounds (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide). In acute

exposures, pulmonary damage may be limited to interstitial inflammation of the alveolar epithelium leading eventually to emphysema or pulmonary fibrosis (Cooper et al. 1982; Dungworth 1989; Saccomanno et al. 1982; Stokinger 1981; Wedeen 1992). In studies of the pulmonary effects of airborne uranium dust in uranium miners (Dungworth 1989; Waxweiler et al. 1983) and in animals (Filippova et al. 1978; Leach et al. 1984; Spiegl 1949; Stokinger et al. 1953), the respiratory diseases reported were aggravated by the insoluble aerosol particles (mine dust) to which these miners were exposed because most of the noncancerous respiratory diseases reported in these studies were consistent with toxicity of inhalable dust particles other than uranium, such as silica (Dockery et al. 1993). This hypothesis is supported by the lack of respiratory diseases in laboratory animal models exposed to aerosols of uranium compounds in the absence of other aerosols (Maynard and Hodge 1949; Maynard et al. 1953; Stokinger et al. 1953; Gilman et al. 1998a; Gilman et al. 1998b; Gilman et al. 1998c). Reports of workers in the uranium-processing industry do not show increased deaths due to diseases of the respiratory system related to exposure to uranium (Brown and Bloom 1987; Cragle et al. 1988; Polednak and Frome 1981; Scott et al. 1972). Respiratory effects reported in workers acutely exposed to uranium hexafluoride were caused by hydrogen fluoride, a potent lung irritant and a spontaneous by-product of uranium hexafluoride (Kathren and Moore 1986; USNRC 1986).

Studies in humans that provide evidence for the radiotoxicity of uranium to the lungs were equivocal and unreliable for use in assessing uranium-specific hazards. The subjects in these studies were also concurrently exposed to known pulmonary toxicants and radiological agents (e.g., radon progeny), as well as to silica dust, which was identified as the etiological agent for silicosis (Dupree et al. 1987; Hadjimichael et al. 1983). Inhalation studies with animals regarding the association of respiratory disease to uranium exposure *per se* were equivocal (Cross et al. 1981a, 1981b, 1982; Leach et al. 1970, 1973, 1984; Morrow et al. 1982; Stokinger et al. 1985). No studies were found that reported respiratory effects in animals following oral or dermal exposure to uranium compounds. Thus, no adverse pulmonary effects from human exposure to uranium *per se* at or near hazardous waste sites are likely. However, prolonged exposure to high levels of insoluble uranium dust, as may occur with uranium miners, millers, and processors, or accidental exposure to high levels of soluble uranium aerosols, especially uranyl fluoride, may damage the lungs by chemical action. These conditions are unlikely at hazardous waste sites; therefore, respiratory effects are unlikely.

Cardiovascular Effects. No reliable studies were identified that associated exposure to uranium with cardiovascular effects in humans. The available studies in animals (rats, mice, guinea pigs, and rabbits) found no adverse cardiovascular effects in animals following inhalation or oral exposures to uranium (Dygert 1949c; Gilman et al. 1998a, 1998b, 1998c; Maynard and Hodge 1949; Stokinger et al. 1953). Although a study in rats that used single intratracheal instillation of 90% enriched soluble uranium salts reported dystrophied blood vessels and enlarged hearts (Filippova et al. 1978), human exposures to such high specific-activity radionuclides at hazardous waste sites are unlikely. No studies were located that reported cardiovascular effects in animals following dermal exposure to uranium compounds. Therefore, no cardiovascular effects are likely from human exposure to environmental levels or to levels expected at or near hazardous waste sites.

Gastrointestinal Effects. A case report of a 5-minute accidental occupational exposure of a male worker in China to fumes of uranium tetrafluoride described signs and symptoms of gastrointestinal distress. These signs and symptoms included loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool (Zhao and Zhao 1990). No gastrointestinal effects were seen in animals given unenriched uranium nitrate in doses as high as 664 mg U/kg/day for 2 years (Gilman et al. 1998a, 1998b, 1998c; Maynard et al. 1949). Gastrointestinal effects are not likely following exposure to uranium at hazardous waste sites.

Hematological Effects. The available human studies (Archer et al. 1973b; Eisenbud and Quigley 1955; Vich and Kriklava 1970) provide no clear evidence that uranium exposure can cause hematological effects in humans. Although the available animal studies provide evidence that very high exposure to uranium compounds may cause disruptions in the blood (Cross et al. 1981b; Dygert 1949b, 1949c, 1949d; Leach et al. 1970, 1973; Ortega et al. 1989a; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949b, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953), others provide evidence of no detectable hematological disturbances (Gilman et al. 1998a, 1998b, 1998c). Adverse effects on the blood are not expected health outcomes from exposure to uranium at the levels found at hazardous waste sites.

Musculoskeletal Effects. No studies have reported effects of uranium on the musculoskeletal system in humans following inhalation, oral, or dermal exposure for any duration. Laboratory animal studies support a lack of toxicological effects on the musculoskeletal system after oral exposures (Gilman et al. 1998a, 1998b, 1998c).

Hepatic Effects. No reliable studies were located regarding the effects of uranium on the liver of humans following inhalation, oral, or dermal exposure for any duration**.** One case report does exist which documents hepatotoxicity in one male who drank 15 g of uranyl acetate (Pavlakis et al. 1996). Uranyl acetate is water soluble and would likely be more quickly absorbed from the gastrointestinal tract than the more insoluble forms of uranium. The patient suffered from increasing liver dysfunction, as evidenced by increased serum ALT, AST, and GGK. Since no liver biopsy sample was obtained, it is difficult to elaborate further on other liver changes that may have occurred. This individual had a history of drug abuse, which may have predisposed him to hepatic toxicity. The liver injury appeared temporary, with no residual signs of hepatotoxicity 6 months after ingestion.

No studies were located regarding the effects of uranium on the liver of animals following dermal exposure for any duration. No indications of liver damage were reported in several animal studies (Dygert 1949c; Pozzani 1949; Rothstein 1949c; Stokinger et al. 1953). However, inhalation exposure to relatively high concentrations of uranium compounds has resulted in mild liver disturbances, although the etiology is not clear. These disturbances include increased bromosulfalein retention, indicative of impaired biliary function, in a chronic-duration inhalation study in dogs (Stokinger et al. 1953); increased urinary catalase, moderate fatty livers, and a slight decrease in hepatic lactate content in rabbits (Roberts 1949; Rothstein 1949c, 1949d); and focal hepatic necrosis in rats (Dygert 1949a; Roberts 1949). Oral exposure of animals to uranium compounds was also accompanied by indications of mild liver damage (Gilman et al. 1998a, 1998c). These indications included microhemorrhagic foci in the liver of rats (Domingo et al. 1987); liver congestion, minimal hepatic lesions, mild degeneration, or fatty infiltration in dogs (Maynard and Hodge 1949); and increased lysosomal activity in dogs (Ortega et al. 1989a). No changes were seen in other dog studies in which the animals were given doses as high as 7,859 mg U/kg/day as the relatively insoluble uranium acetate dihydrate for 30 days (Maynard and Hodge 1949). Anisokaryosis, vesiculation, increased portal density, and perivenous vaculolation were observed in rats (Gilman et al. 1998a), while accentuation of zonation, variation in hepatocellular nuclear size, nuclear pyknosis, and excessive cytoplasmic vacuolization were observed in rabbits (Gilman et al. 1998c). The data presented here suggested that uranium is a hepatotoxicant by the inhalation and oral exposure routes in both humans (limited data set) and laboratory animals. Uranium disrupts general hepatocellular function and cellular permeability; however, no mechanism for these effects has been identified from any of these studies. On the basis of the available data, effects on the liver can occur as a result of human exposure to uranium compounds. However, human and animal studies indicate that the

liver is an order of magnitude less sensitive than the kidney by either inhalation (Dygert 1949a, 1949d; Pozanni 1949; Rothstein 1949c; Stokinger 1953) or oral (Gilman et al. 1998a, 1998c; Maynard and Hodge 1949; Pavlikis et al. 1996) routes, for all exposure durations. Thus, it is highly unlikely that exposure to uranium compounds near hazardous waste sites could result in liver damage.

Renal Effects. Uranium has been identified as a nephrotoxic metal, exerting its toxic effect by chemical action mostly in the proximal tubules in humans and animals. There is sufficient information with high exposures to both soluble and insoluble uranium to permit the conclusion that uranium has a low order of metallotoxicity in humans in view of the high levels to which the subjects were exposed. The negative findings regarding renal injury among workers exposed to insoluble compounds are particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955).

Several epidemiologic studies found no increased deaths in uranium workers due to renal disease (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). Also, case studies showed that workers accidentally exposed to high levels of uranium did not have renal damage even up to 38 years postexposure (Eisenbud and Quigley 1956; Kathren and Moore 1986). However, one study on the kidney function of uranium mill workers chronically exposed to soluble uranium revealed renal tubular dysfunction as manifested by mild proteinuria, aminoaciduria, and a dose-related clearance of β_2-microglobulin relative to that of creatinine. Serum β_2-microglobulin was also elevated in the serum of 22 of the 23 workers tested. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the yellowcake (insoluble) drying and packaging area (Saccomanno et al. 1982; Thun et al. 1985). The data from this study were indicative of reduced protein resorption in the proximal renal tubules consistent with the observed renal toxicity of uranium in animals. Two case reports of accidental occupational exposures to high concentrations of both soluble and insoluble uranium by inhalation or dermal routes described clinical findings of a decreased glomerular filtration rate as manifested by decreased urinary output and significantly elevated urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and phenolsulfonpthalein. Renal function rapidly returned to normal in days (Zhao and Zhao 1990). Acute nephrotoxicity was attributed to a large oral intake of uranyl acetate (Pavlakis et al. 1996). Similarly, the results of animal studies indicated that nephrotoxicity is the most consistent and sensitive adverse effect following inhalation (Dygert 1949a, 1949b, 1949c, 1949d; Filippova et al. 1978; Gilman et al. 1998a, 1998b, 1998c Leach et al. 1970, 1973, 1984; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein

1949a, 1949c, 1949d; Spiegl 1949; Sprague 1949; Stokinger et al. 1953), oral (Domingo et al. 1987; Gilman et al. 1998a, 1998b, 1998c; MacDonald-Taylor 1992; Maynard and Hodge 1949; Ortega et al. 1989a), or dermal (De Rey et al. 1983; Orcutt 1949) exposures to uranium compounds. These nephrotoxic effects are consistent with the metallotoxic action of uranium in the kidneys (Goodman 1985). The pathogenesis of the kidney damage in animals indicates that regeneration of the tubular epithelium occurred following discontinuation of exposure to uranium (Bentley et al. 1985; Dygert 1949b; Maynard and Hodge 1949; Pozzani 1949; Rothermel 1949; Rothstein 1949c; Spiegl 1949; Stokinger et al. 1953). Thus, exposure to the soluble compounds of uranium at or near hazardous waste sites could result in kidney damage. Measurement of uranium in air, soil, and water at or near the site is necessary to predict the likelihood of renal effects.

The following MRLs have been calculated for exposure to uranium based on kidney effects:

- an intermediate-duration MRL of $8x10^{-3}$ mg/m^3 for inhalation exposure to insoluble compounds of uranium is based on renal tubule lesions in dogs (Rothstein 1949b);
- an intermediate-duration MRL of $4x10^{-4}$ mg/m^3 for inhalation exposure to soluble compounds of uranium is based on renal tubule lesions in dogs (Rothstein 1949a);
- a chronic-duration MRL of $3x10^{-4}$ mg/m^3 for inhalation exposure to soluble compounds of uranium is based on renal tubule lesions in dogs (Stokinger et al. 1953);
- an intermediate-duration MRL of $2x10^{-3}$ mg/kg/day for oral exposure to soluble compounds of uranium is based on renal tubule lesions in rabbits (Gilman et al. 1998b);

See the MRL discussion earlier in this section and in the MRL Worksheets in Appendix A for further details on the derivation of these MRLs.

Endocrine Effects. No endocrine effects were reported in humans following inhalation, oral, or dermal exposure to uranium compounds. No endocrine effects were reported in most of the available studies of animals following inhalation or oral exposure to uranium compounds (Gilman et al. 1998a, 1998b, 1998c; Ortega et al. 1989a; Maynard and Hodge 1949; Stokinger et al. 1953). A later study by Gilman et al. (1998a) using uranyl nitrate also identified endocrine organ changes that were limited to multifocal reductions in follicular size, increased epithelial cell height, and decreased amounts and densities of colloid in the thyroids of male but not female rats. Endocrine effects are not a significant health concern to individuals living at or near hazardous waste sites containing uranium.

Dermal Effects. No significant dermal effects were observed in animals given inhalation or oral doses of uranium compounds (Spiegl 1949; Stokinger et al. 1953). However, dermal application of uranium compounds resulted in mild skin irritation, severe dermal ulcers, or superficial coagulation necrosis and inflammation of the epidermis in rabbits (Orcutt 1949). Dermal application resulted in swollen, vacuolated epidermal cells and damage to hair follicles and sebaceous glands in rats (De Rey et al. 1983). The effects or symptoms of acute dermal exposure to ionizing radiation included erythema (redness of the skin) and epilation (loss of hair) (Upton 1993). The alpha particle emitted by uranium will not penetrate the dead keratinized outer layer of the skin, so there is minimal concern for dermal effects from skin contact with uranium. Dermal effects were not seen in studies of uranium miners, millers, and processors. The observed skin damage reported in animals dermally exposed to excessive quantities of uranium compounds is not expected to occur in human exposures at hazardous waste sites. Such exposures, if they occur, are expected to be at or less than the levels at which uranium miners, millers, and processors are exposed (levels at which no attributable dermal health effects were reported).

Ocular Effects. No ocular effects attributable to uranium exposure were reported in the available human studies. In animal studies, dogs exposed to 13 mg U/m^3 as uranium hexafluoride for 30 days exhibited encrusted eyes and conjunctivitis prior to death. However, these signs were considered nonspecific indications of poor health by the investigators of the study (Spiegl 1949). Consequently, no ocular effects are expected from human exposure to uranium compounds.

Body Weight Effects. Body weight loss was not reported in any of the human studies regarding inhalation, oral, or dermal exposure to uranium compounds. Similarly, the available studies in animals that evaluated this end point did not find any significant changes following inhalation exposure to uranium compounds (Cross et al. 1981b; Dygert 1949c, 1949d; Leach et al. 1970, 1973; Pozzani 1949; Rothermel 1949; Rothstein 1949a, 1949b, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Similar lack of body weight effects were found in rats in 28- and 91-day using uranium nitrate in the drinking water (Gilman et al. 1998a). The initial or reversible loss of body weight observed in animals exposed to high concentrations of uranium in the diet in acute-, intermediate-, and chronic-duration studies was accompanied by decreased food consumption due to taste aversion (Maynard and Hodge 1949, 1953; Tannenbaum and Silverstone 1951). This initial effect reversed, and the animals returned to their normal body weight as normal food intake resumed. Thus, the changes in body weight seen in such studies may be due more to reduction in food consumption due to bad taste than to uranium-specific toxicity. This

effect may not be relevant to humans. It is more likely that significant weight loss in rabbits following application of excessive dermal doses (as high as 1,917 mg U/kg) (Orcutt 1949) may be a response to exceeding the maximally tolerated dose in these animals and consequently overwhelming the physiological mechanisms in these species (Orcutt 1949). Therefore, no significant effect on body weight is expected from human exposure to uranium compounds at or near hazardous waste sites.

Metabolic Effects. No studies were located regarding the metabolic effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation, oral, or dermal exposure to uranium and uranium compounds. Consequently, it is not known whether human exposure to uranium and uranium compounds could result in adverse metabolic effects; however, such effects would not be anticipated, based on the absence of endocrine effects.

Other Systemic Effects. No studies were located that reported other systemic effects in humans or animals following inhalation, oral, or dermal exposure to uranium. Consequently, no other systemic effects are expected from human exposure to uranium compounds at or near hazardous waste sites.

Immunological and Lymphoreticular Effects. No adverse immunological or lymphoreticular effects were reported in human studies following exposure to uranium through the inhalation, oral, or dermal route for any duration (Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981; Vich and Kriklava 1970). Similarly, no significant uranium-induced immunological or lymphoreticular changes were observed in animals exposed to uranium for acute, intermediate, or chronic durations (Filippova et al. 1978; Gilman et al. 1998a, 1998b, 1998c; Leach et al. 1970, 1973; Malenchenko et al. 1978; Maynard et al. 1953; Stokinger et al. 1953; Tannenbaum and Silverstone 1951). Sinus hyperplasia of the spleen was noted in rats in one 91-day uranium nitrate drinking water study (Gilman et al. 1998a). No significant immunological or lymphoreticular injury is expected from human exposure to uranium compounds at or near hazardous waste sites.

Neurological Effects. Although no neurological functions were evaluated in most of the available human studies, no damage to structures of the central or peripheral nervous system and no overt neuropathology were reported in humans following exposure to natural or enriched uranium compounds by the inhalation, oral, or dermal route (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988;

Kathren and Moore 1986; Polednak and Frome 1981; Reyes et al. 1984; USNRC 1986). Clinical signs in one man following acute exposure to uranium did include dizziness and anorexia 6 days after exposure for 5 minutes to uranium tetrafluoride by inhalation (Zhao and Zhao 1990), and may have been related to rapidly developing renal disease. No etiology could be determined for increased central and peripheral nervous system diseases found in workers in a nuclear fuels fabrication plant (Hadjimichael et al. 1983). A series of studies by Gilman et al. (1999a, 1998b, 1998c) reported no brain lesions associated with ingestion of uranium in the drinking water. However, in other high-dose animal studies, neurological signs were reported in dogs, cats, rats, and guinea pigs. These signs included instability of gait indicative of neurological dysfunction in dogs and cats (Dygert 1949a); severe muscle weakness and lassitude from inhalation exposures in dogs and cats (Rothstein 1949a); central cholinergic neurological symptoms (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos) in rats from oral exposures (Domingo et al. 1987); and irritability, hyperactivity, upset equilibrium, rigidity of limbs, and respiratory arrest in rabbits from 4-hour dermal exposures (Orcutt 1949). However, no neurological effects were observed in rabbits orally exposed to 20 times larger oral doses of the same compound for 91 days. In view of the findings of the human and animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in damage to the nervous system.

Recent studies suggest that intramuscular deposition of uranium metal may result in neurological effects. Implantation of depleted uranium pellets in rats resulted in measurable uranium in the brain at 6–18 months after implantation (Pellmar et al. 1999a) and was accompanied by electrophysiological changes in hippocampal slices from the treated animals at 6 months (Pellmar et al. 1999b). In addition, military veterans with retained depleted uranium shrapnel fragments had lowered performance scores on computerized tests assessing performance efficiency which correlated with their urinary uranium levels (McDiarmid et al. 1999a). The etiology of these effects is unclear, although central nervous system toxicity due to other heavy metals (e.g., lead, mercury) is well documented. Further research is needed to confirm these results and determine the relevance of the effects from this unique exposure pathway to inhalation, oral, and dermal exposure.

Reproductive Effects. The existing human data from studies of uranium miners, millers, and processors (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and most data from animal studies (Gilman et al. 1998a, 1998b; Leach et al. 1970; Llobet et al. 1991; Paternain et al. 1989) do not associate reproductive effects with uranium exposure.. Relatively high doses of uranium compounds (which also

produced significant mortality in some cases) have resulted in some reproductive abnormalities manifested as significantly reduced sperm counts (Lloblet et al. 1991), reduced implantations and increased fetal resorptions and dead fetuses, maternal (reduced weight gain and food consumption, increased relative liver weight) and fetal toxicity (Domingo et al. 1989a); testicular lesions and degeneration and decreased testes weight (at near-lethal doses for long periods) (Malenchenko et al. 1978; Maynard et al. 1953); and reduced litter size (at a dose that produced 16% mortality) (Maynard et al. 1953) following intake of uranium compounds. However, no reproductive effects were found in a series of 28-day and 91-day uranium drinking water studies in rats and rabbits (Gilman et al. 1998a, 1998b, 1998c; Paternain et al. 1989).

In view of the lack of findings of reproductive effects in uranium miners, millers, and processors in numerous human studies and the equivocal findings in high-dose animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in interference with normal reproduction.

Developmental Effects. The present theories on the susceptibility of cells (with a high mitotic index such as are found in the embryo, fetus, and neonate) to damage by the DNA-adducting chemical action of uranium (as a heavy metal) (Cooper et al. 1982; Dungworth 1989; Stokinger 1981; Wedeen 1992) and ionization by high-LET, high specific-activity radiation (BEIR 1980, 1988, 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) suggest that uranium may potentially interfere with normal development and may be teratogenic. However, no studies were located regarding the chemical or radiological effects of uranium on development in humans or animals following inhalation or dermal exposure for any duration.

Evidence for potential developmental toxicity is provided by results from oral animal studies in which the following effects were reported for uranyl acetate: increased fetal mortality, reduced survivability, and reduced growth (Paternain et al. 1989); decreased litter size, decreased viability and lactation indices, and pup liver weights (Domingo et al. 1989b); reduced fetal body weight and length, an increased incidence of stunted fetuses, increases in external and skeletal malformations and developmental variations, an increased incidence of cleft palate, underdeveloped renal papillae, and bipartite sternebrae, reduced or delayed ossification of the hind limb, fore limb, skull, and tail, an increase in the relative brain weight of the offspring, and reduced viability and lactation index (Domingo et al. 1989a); and embryotoxicity (Paternain et al. 1989). These effects were seen at relatively high doses far above any plausible human exposure.

The investigators of a study in which relative liver weights were significantly decreased at all exposure levels ($p<0.05$ in the 0.028–0.28 mg U/kg/day group and $p<0.01$ in the 2.8–28 mg U/kg/day group) in offspring of rats exposed to 0.028, 0.28, 2.8, or 28 mg U/kg/day for 30 days concluded that these effects were not uranium induced. Decreases in the relative liver weights (noted at 0.028 mg U/kg/day) and relative brain weight (noted only at 0.28 mg U/kg/day) were not considered significant effects of uranium exposure since the investigators concluded that the NOAEL for this study was 2.8 mg U/kg/day for fetotoxicity with a LOAEL of 28 mg U/kg/day (Domingo et al. 1989b). In addition, there is a lack of plausible biological validity for hepatic effects at such low doses of uranium because the other available studies with rats in which uranium acetate was administered orally for a similar duration either showed no significant effect on the liver (Maynard and Hodge 1949) at a uranium acetate dosage of 7,859 mg U/kg/day or resulted in only liver congestion (Ortega et al. 1989a) at a uranium acetate exposure of 9 mg U/kg/day. Further, the kidney rather than the liver is the most sensitive organ of uranium toxicity in both humans (Thun et al. 1985) and animals (Domingo et al. 1987; Maynard and Hodge 1949; Ortega et al. 1989a). No kidney effects were reported in this study. In previous research, the same investigators (Domingo et al. 1989a) found the opposite effect (increased relative liver weight) at all dose levels.

In view of the lack of findings of developmental effects in the offspring of uranium miners, millers, and processors in numerous human studies and the equivocal findings in animal studies, it is doubtful that human exposure to uranium compounds at or near hazardous waste sites could result in interference with normal development.

Genotoxic Effects. No information was located showing metallotoxic or radiotoxic effects of uranium on genetic material in humans or animals following dermal exposure for any duration. In human studies, chromosomal aberrations and aberrant DNA consistent with radiation damage were found in uranium miners. However, the etiology of the effects on the chromosome and DNA could not be determined because the miners were concurrently exposed to other radioactivity (radon progeny), smoking, and potentially genotoxic microorganisms (genus *Aspergillus* and *Penicillium*).

Because uranium is a predominantly an alpha-emitting element, current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a concern for genotoxicity from uranium's radioactivity (BEIR 1980, 1988, 1990; Leach et al. 1970; Morris et al. 1990; Muller et al. 1967; Otake and Schull 1984; Sanders 1986; Stokinger et al. 1953; UNSCEAR 1982, 1986, 1988) (see Appendix D

for a review of the hazards associated with radionuclide exposure). However, uranium does not distribute to or accumulate in the gonads in any appreciable amount.

In animal studies, mice injected with doses ranging from 0.05 to 1.0 µg U/testis as enriched uranium fluoride showed a general tendency for an increase in chromosome breaks with an increasing dose of enriched uranyl fluoride. At high-dose levels, the statistically significant difference of break frequencies between treated and control mice disappeared 60 days after treatment (Hu and Zhu 1990).

A study that investigated the effects of uranyl nitrate hexahydrate on viability, cell cycle kinetics, micronuclei, chromosomal aberrations, and sister-chromatid exchanges in Chinese hamster ovary cells found an increased frequency of micronuclei, sister-chromatid exchanges, and chromosomal aberrations leading to the conclusion that uranyl nitrate hexahydrate was genotoxic under the conditions of the assay (Lin et al. 1993).

However, it is unlikely that humans could be exposed at hazardous waste sites to such high specific-activity radionuclides through the routes described in these studies. Table 2-9 lists the genotoxic effects of uranium *in vivo* and Table 2-10 lists the genotoxic effects of uranium *in vitro*.

Recent studies suggest that intramuscular deposition of uranium metal may result in genotoxic effects in animals. Implantation of depleted uranium pellets in rats resulted in an increase in the mutagenic potential of urine towards the Salmonella tester strain TA98 (Miller et al. 1998a). Responses were dose- and time-dependent and strongly correlated with urine uranium levels. In an *in vitro* study, uranyl chloride prepared from depleted uranium transformed immortalized human osteoblastic cells to a tumorigenic phenotype (Miller et al. 1998b). The etiology of these effects is unclear at this time. Further research is needed to confirm these results and determine the relevance of the effects from this unique exposure pathway to inhalation, oral, and dermal exposure.

Cancer. There has been interest in the potential carcinogenicity of uranium, which emits alpha-particle radiation, although natural, depleted, or enriched uranium or uranium compounds have not been evaluated in rodent cancer bioassays by any route by the NTP (BEIR 1980, 1988, 1990; Hahn 1989; Otake and Schull 1984; Sanders 1986; UNSCEAR 1982, 1986, 1988). However, there is no unequivocal evidence that inhalation, oral, or dermal exposure induces cancers in humans because it is difficult to isolate the

Table 2-9. Genotoxicity of Uranium *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference
Mammalian systems:				
Human	Chromosomal aberration	Inhalation	+	Martin et al. 1991
Human	Sister chromatid exchange	Inhalation	+	Martin et al. 1991
Mouse (BALB/c)	DNA damage	Intraperitoneal	+	Hu and Zhu 1990

– = negative result
+ = positive result

Table 2-10. Genotoxicity of Uranium *In Vitro*

Species (test system)	End point	Result	Reference
Eukaryotic cells:			
Human peripheral blood lymphocytes	Chromosomal aberration	+	Fajgelj et al. 1992
Chinese hamster cells	Sister chromatid exchange	+	Lin et al. 1993
Chinese hamster cells	Chromosomal aberrations	+	Lin et al. 1993
Chinese hamster cells	Micronucleus test	+	Lin et al. 1993

– = negative result
+ = positive result

cancer risk that may be specific to exposure to uranium and other substances such as tobacco smoke, radon and its decay products, radium, thorium, silica and other dusts, and diesel engine exhaust fumes to which the human subjects of these studies were concurrently exposed (Archer et al. 1973a, 1973b; Auerbach et al. 1978; Band et al. 1980; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Lundin et al. 1969; Polednak and Frome 1981; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1982, 1988; Samet et al. 1984, 1986; Sanders 1986; Waxweiler et al. 1983; Whittemore and McMillan 1983; Wrenn and Singh 1983). Long-term animal studies with both natural and enriched uranium were negative (Cross et al. 1981b; Leach et al. 1970, 1973, 1984; Maynard and Hodge 1949; Maynard et al. 1953; Spiegl 1949; Stokinger et al. 1953; Tannenbaum and Silverstone 1951) or equivocal (Filippova et al. 1978; Leach et al. 1973; Mays et al. 1985) for carcinogenicity. No information was located on the cancer effects in humans or animals following dermal exposure to uranium for any duration.

The potential for carcinogenicity by administration by parenteral routes has been investigated in one animal study. Although the parenteral route is an unlikely route of exposure at hazardous waste sites, it is analogous to the condition in which uranium compounds enter cuts, wounds, abrasions, and ulcers in large quantities. That portion which enters the systemic circulation is expected to distribute in the same manner as uptakes by inhalation or ingestion, while any portion that remains at the entry site could produce large localized concentrations which are orders of magnitude larger than those calculated based on body weight. Rats that received 50 mg U (34 nCi or 1,200 Bq) as powdered metallic uranium injected as a single dose into the marrow cavity of the femur developed 11 injection-site sarcomas in 33 rats, 30 of which survived the minimal latent period of 6 months (Hueper et al. 1952). Other rats given intrapleural administration of metallic uranium equivalent to approximately 574 nCi/kg (21,238 Bq/kg or 860 mg U/kg) exhibited 2 sarcomas originating from the chest wall among 33 rats treated; 2 of the 13 sarcomas were bone-forming, and 6 produced metastases. All sarcomas either surrounded uranium deposits or were in the immediate vicinity of them. None of the 13 sarcomas seemed to originate from the endosteum. The sarcomas appeared either to be of periosteal origin or to stem from mesodermal elements of the thigh muscle. The investigators of the study were unable to ascertain whether the sarcomas were due to a metallocarcinogenic action of uranium or were caused by a radiocarcinogenic effect of this radioactive chemical. However, these observations demonstrate that localized uranium deposits in the tissues of rats created a high concentration of uranium in circumscribed areas, and the prolonged action of the uranium on cells in the immediate vicinity of such foci exert a definite carcinogenic effect (Hueper et al. 1952).

The BEIR IV report concluded that "...exposure to natural uranium is unlikely to be a significant health risk in the population and may well have no measurable effect" (BEIR IV 1988).

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). There may also be differences in excretion, particularly in the newborn

who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Specific information is not available on whether children are more susceptible than adults to the effects of uranium. No reports were located describing toxicity in children as the result of uranium exposure. It is probable, however, that if exposure levels were high enough, signs of renal toxicity would be observed similar to those seen in adults exposed accidentally (Zhao and Zhao 1990) or intentionally (Pavlaikis 1996). No reports are available of studies where toxic responses of young animals to uranium were directly compared to those of adults.

No studies are available on whether exposure to uranium affects development in humans. The information from animal studies is limited to the oral route in a single species, and only one study examined structural malformations. Uranium has not caused teratogenic effects, although some developmental effects have been reported in mice (Domingo et al. 1989a, 1989b; Paternain et al. 1989). These effects generally occurred at gavage doses $\geq$6 mg U/kg/day in a soluble form as uranyl acetate. At doses of 14 mg U/kg/day but not 6 mg U/kg/day, embryolethality (increased total and late resorptions, decreased number of live fetuses) was observed on gestation day 13 in dams exposed from 14 days prior to mating through gestation (Paternain et al. 1989). Gavage exposure over gestation days 6–15 resulted in an increased incidence of skeletal abnormalities (bipartite sternebrae, reduced and/or delayed ossification) at 14 and 28 mg U/kg/day and cleft palate at 6, 14, and 28 mg U/kg/day (Domingo et al. 1989a). Underdeveloped renal papillae were also observed but were not dose-related. Exposure of dams from late pregnancy (gestation day 13) continuing throughout lactation (21 days postpartum) resulted in reduced pup viability at 28 mg U/kg/day, but not at lower doses (Domingo et al. 1989b). Postpartum

developmental events (pinna attachment, eye opening, incisor eruption) were unaffected at all doses. While developmental toxicity can be produced in animal models, the doses required are relatively high compared to known human exposures and are similar to a dose of 14.3 mg U/kg of uranyl nitrate that produced nausea, vomiting, and diarrhea in one human (Butterworth 1955).

Information on the pharmacokinetics of uranium in children is very limited. Since the skeletons of children are growing (higher rate of bone formation), it is possible that a higher fraction of circulating uranium will be deposited in bone than in adults. A study of uranium content in bone from three age groups (<13, 13–20, 20–25 years old) reported somewhat higher uranium content in the youngest compared to the oldest age group (approximately 1.5–3 fold); however, there were only 2–4 subjects in each group and the differences were not statistically significant (Broadway and Strong 1983). The fractional absorption of uranium by the oral route was higher in neonatal swine and rats than in adult animals (Sullivan 1980b; Sullivan and Gorham 1982).

Transfer of uranium across the placenta was investigated in an animal study, but no information is available for humans. In the animal study, only 0.01–0.03% of an intravenous dose of uranium to rat dams crossed the placenta (Sikov and Mahlum 1968); thus if an inhalation, oral, or dermal exposure was sufficient to raise the blood uranium level, a very limited amount of uranium might cross the placenta. No studies were located regarding uranium in breast milk. Based on the chemical properties of uranium, it seems unlikely that there would be preferential distribution from the blood to this high-fat compartment. It is not known if uranium has any effect on the active transport of calcium into breast milk. Most of the adult body burden of uranium is stored in bone (ICRP 1979, 1995, 1996). It is not known if maternal bone stores of uranium (like those of calcium and lead) are mobilized during pregnancy and lactation.

Age-related differences in the pharmacokinetics of uranium have been incorporated into existing PBPK models (ICRP 1995, 1996) so that they can be applied to children. Two adjustments were made:

1. The value for the fractional absorption of ingested uranium (f_1) was adjusted from the adult value of 0.02 (2%) to a value of 0.04 (4%) for children under the age of 1 year. This adjustment was made based on animal data (Sullivan et al. 1980b; Sullivan and Gorham 1982) and information on postnatal changes in the human gastrointestinal tract. For ages over 1 year, the adult value for fractional absorption was used.

2. Parameters for transfer of uranium into and out of bone were assumed to be proportional to those of alkaline earth elements such as calcium (the UO_2^{2+} ion can substitute for the Ca^{2+} ion at bone surfaces). Age-specific bone turnover rates developed for a generic alkaline-earth model (ICRP 1993) were incorporated into the uranium model to predict distribution to the tissues. As a result of this change, a greater proportion of uranium distributes to bone and a lesser proportion to soft tissues at ages under 25 years, compared to adults.

The mechanism for the renal toxicity observed in cases of adult exposure to uranium is believed to be due to the retention of uranium in the kidney. This is the result of the reabsorption of bicarbonate from the ultrafiltrate in the proximal tubule and the resulting release of the UO_2^{2+} ion from a bicarbonate complex. Newborn humans have relatively inefficient tubular secretion and reabsorption compared to older children or adults, and whether this would increase or decrease the susceptibility of newborns to uranium toxicity is not known.

2.7 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium, or nonessential substances in all diets such as aluminum and uranium. Biomarkers of exposure to uranium are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by uranium are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in dose excretion, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Uranium

Biomarkers of exposure to uranium include the chemical or radiological detection of uranium in the urine because uranium absorbed through the oral, dermal, and inhalation routes is excreted in urine mostly as uranyl ions (Ballou et al. 1986; Cooper et al. 1982; Downs et al. 1967; Leach et al. 1984; Morrow et al. 1982; Stradling et al. 1984, 1987; West and Scott 1969; Wrenn et al. 1985). Uranium urinalysis data have been shown to correlate with airborne uranium exposures when averaged over a period of time when the ingested quantity is insignificant. Thus, this method of analysis can be used to verify the adequacy of air sampling and as a noninvasive method for exposure estimates (Chase 1989; Davis 1985; Schieferdecker et al. 1985; Thind 1987). Typical chemical detection methods for uranium include fluorimetry and kinetic phosphorescence analysis (KPA), while the primary radiological method is alpha spectroscopy. Some of the more capital-intensive and sophisticated techniques that will allow isotope quantification in very small fecal, urine, or tissue samples are isotope dilution alpha spectrometry; neutron activation analysis; and isotope-dilution, inductively coupled plasma, and atomic absorption versions of mass spectrometry. The mass spectrometric, KPA, and neutron activation techniques are probably the most sensitive and accurate for the quantification of uranium isotopes (Wessman 1984).

According to *USNRC Regulatory Guide 8.22*, the acceptable methods for the quantification of uranium in urine must have a detection limit of 5 µg/mL and a precision of 30% (Kressin 1984). A urinary concentration >100 µg/L is indicative of recent absorption, while a concentration of <40 µg/L may be due either to slow uptake from the site of absorption or to bone mobilization (Butterworth 1955). Variations in background levels of uranium from drinking water in different locations may also result in higher or lower urinary concentrations of uranium.

Twenty-four-hour urine samples are preferable for analysis; spot samples gave accurate results when corrected for creatinine content, but only for individuals excreting relatively large amounts of uranium (McDiarmid et al. 1999b).

Uranium content in soft tissue and bone could also be used as biomarkers of exposure to uranium since uranium also distributes to these tissues and other organs (Ballou et al. 1986; Diamond et al. 1989; Leach et al. 1973, 1984; Morris et al. 1990; Morrow et al. 1972; Stokinger et al. 1953; Walinder 1989; Wrenn et al. 1987). Although soft tissues and bone are the most frequently analyzed biological media after urine and feces, these tissues are usually available for analysis only at autopsy. Therefore, this method is impractical and not used for routine screening purposes.

2.7.2 Biomarkers Used to Characterize Effects Caused by Uranium

Currently, there are no available biomarkers for specific exposure to the metallotoxic or radiotoxic effects of uranium.

Functional damage to the kidneys has been documented in humans (Pavlakis et al. 1996; Thun et al. 1985; Waxweiler et al. 1981a; Zhao and Zhao 1990) and in animal (Leach et al. 1970, 1973, 1984; Morrow et al. 1982; Stokinger et al. 1953) studies. Although not specific to uranium toxicity, urinary catalase as an indicator of renal damage (Luessenhop et al. 1958) could be used in conjunction with other signs of renal tubular dysfunction, including mild proteinuria, aminoaciduria, and clearance of β_2-microglobulin relative to that of creatinine, as a battery of indicators of biomarkers of exposure to uranium (Saccomanno et al. 1982; Thun et al. 1985).

Very high doses of uranium may interfere with liver function in humans (Pavlaikis et al. 1996), but renal effects are far more sensitive. No specific biomarker is currently available for the liver as a target of uranium toxicity. Because uranium has no appreciable effect on the nervous system, no biomarkers of effect are needed for this end point. For more information on biomarkers for renal effects of chemicals, see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (ATSDR/CDC 1990). Simultaneous analysis of multiple parameters, such as urinary glucose, alkaline phosphatase, and β_2-microglobulin, which may be more specific to proximal tubular damage (Limson-Zamora et al. 1996) should be considered for evaluating subjects in future studies.

2.8 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding the modulation of the toxicity of uranium by other chemicals or vice versa. It is possible that co-exposure to other heavy metal nephrotoxicants (e.g., lead, cadmium) could have an additive effect on uranium toxicity.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to uranium than will most persons exposed to the same level of uranium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of uranium, or compromised function of target organs affected by uranium. Populations who are at greater risk due to their unusually high exposure to uranium are discussed in Section 5.6, Populations with Potentially High Exposure.

Populations susceptible to uranium toxicosis would include people with impaired renal function. People with stomach ulcers are thought to have elevated absorption of some toxic metals and might be unusually susceptible to uranium toxicity. The potential for children's susceptibility is discussed in Section 2.6.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing the toxic effects of exposure to uranium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to uranium. When specific exposures have occurred, poison control centers, health physicists, and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to uranium:

2.10.1 Reducing Peak Absorption Following Exposure

No specific recommendations have been reported for reducing the peak absorption following acute exposure to uranium. However, because uranium forms complexes with the bicarbonate ion (Cooper et al. 1982), there is a role for oral sodium bicarbonate in the mobilization of systemic uranium, thereby preventing uptake by critical tissues (kidney, bone).

2.10.2 Reducing Body Burden

Administration of bicarbonate is applicable to reducing uranium body burdens from acute exposures. Bicarbonate ions complex with uranium and alkalize the blood, both of which enhance the excretion from the kidneys by glomerular filtration (Cooper et al. 1982) and such an application was described in a case of prophylactic treatment (Fisher et al. 1991). Experimental evidence in animals indicates that chelation therapy may reduce the body burden of uranium. Several compounds were found to enhance the urinary and fecal excretion of uranium, if administered soon after uranium exposure. When given immediately after exposure to uranium, Tiron resulted in the greatest reduction in renal and bone levels of uranium and acute lethal effects in animals (Domingo et al. 1992; Ortega et al. 1989a). None of the chelating agents affected bone levels of uranium when given 24 hours or more after exposure to uranium (Domingo et al. 1992). Bicarbonate treatment is also limited to very near-term exposures.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Treatment for uranium poisoning is typically in response to a known accidental exposure to uranium and is largely asymptomatic. One study found that Tiron® (sodium 4,5-dihydroxybenzene-1,3-disulphonate), gallic acid, and DTPA (diethylamine-tetramine-pentaacetic acid) were the most effective chelating agents among those tested for binding systemic uranium and removing it from the body following large acute intraperitoneal injections (Ortega et al. 1989). However, another study which tested Tiron® alone and in conjunction with either DTPA or EDHPA (ethylenediamine-N,N'-bis[2-hydroxyphenylacetic acid]) found that it reduced the uranium body burden no more than about 35%, indicating that the administration of Tiron® is of limited practical value for the treatment of uranium exposures that do not greatly exceed the permitted intake level (Stradling et al. 1991).

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of uranium 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 uranium.

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

2.11.1 Existing Information on Health Effects of Uranium

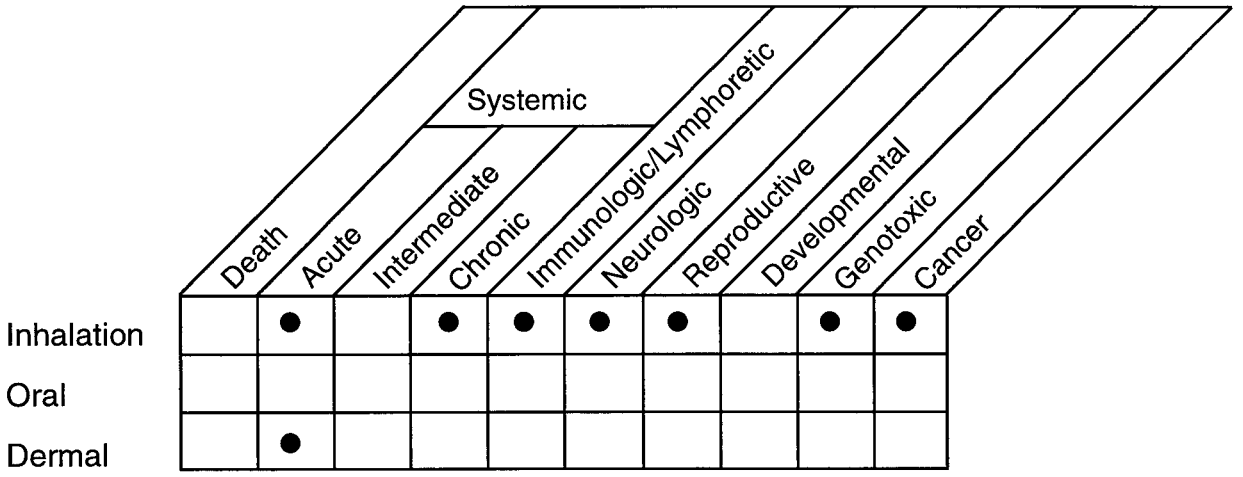
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to uranium are summarized in Figure 2-10. The purpose of this figure is to illustrate the existing information concerning the health effects of uranium. Each dot in the figure indicates that one or more

studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

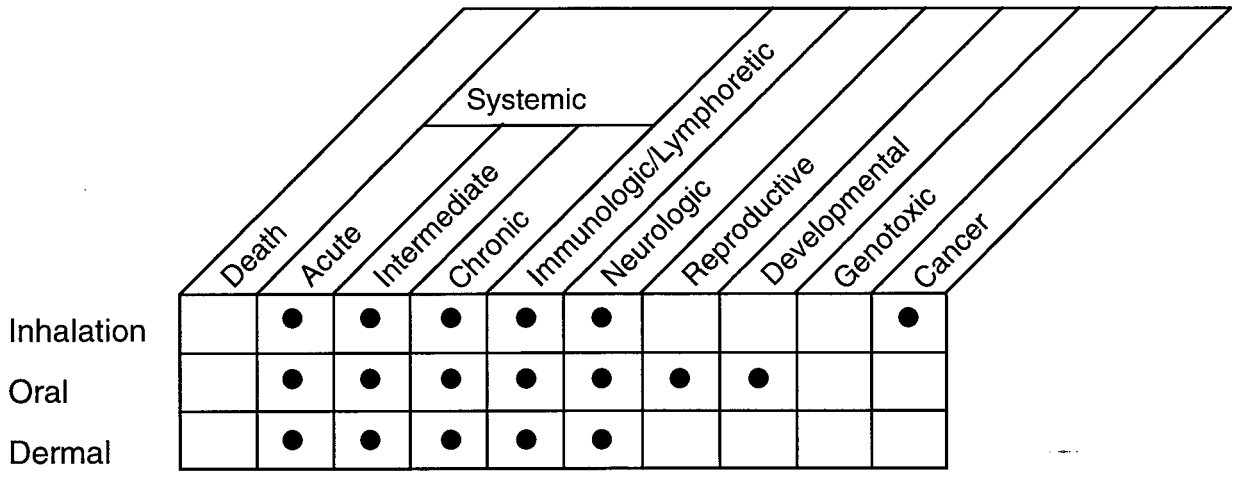
Figure 2-10 depicts the existing health effects information on uranium for a specific route and duration of exposure. There is a lack of information regarding the health effects in humans from ingested uranium. Similar information from dermal exposures is also scarce; only two studies were located in this respect. Several available studies that investigated the health effects in humans of inhalation exposure to uranium are limited to occupational settings (miners, millers, processors). The subjects of some of these studies were also concurrently exposed to other potentially toxic substances, rendering it difficult to establish the etiology for the effects reported in these studies; however, studies of processors who were not concurrently exposed to those toxicants are useful in this regard. Consequently, indications of the cancer-inducing potential of uranium in these latter workers were useful in making a determination that uranium exposure by normal routes of exposure is unlikely to be carcinogenic. Although three human studies presented limited evidence of reproductive effects (damage to sex chromosomes) in uranium mine workers, no empirical evidence was presented for evaluation. Information on the systemic effects of uranium through the inhalation, oral, and dermal routes of exposure are available. However, there is limited information regarding the reproductive and developmental effects of uranium in animals; no multigenerational studies are available. In addition, because the data from some critical studies were not clearly or sufficiently presented, the data were inadequate for use in the development of acute-duration inhalation or acute- and chronic-duration oral MRLs; however, sufficient information is available on the effects of chronic oral exposure to conclude that the intermediate-duration MRL is protective for chronic exposure. An NTP cancer bioassay and an EPA IRIS cancer classification are not available for uranium.

Available long-term animal studies characterize uranium's cancer potential as low. Definitive studies regarding the genotoxicity of uranium *in vitro* or *in vivo* are lacking. In general, there are several robust human epidemiological studies of miners, millers, and processors which strongly indicate that uranium is not carcinogenic by the inhalation route unless mixed with toxicants and carcinogens such as silica dust, diesel fumes, radon progeny, and cigarette smoke. Animal studies involving large doses have also found no

Figure 2-10. Existing Information on the Health Effects of Uranium



Human



Animal

● Existing Studies

cancer, and the one study which superimposed a large dose of external ionizing radiation concluded that the respiratory effects which were noted were due to chemical and not radiological action. Any research investigating the radiotoxicity of uranium may be of limited importance because the radiation from natural and depleted uranium has not been shown to present a substantial radiological hazard; however, this may not be the case for the less available high specific activity isotopes such as ^{233}U and ^{234}U, that are formed during energy production or associated with weapons-grade uranium.

2.11.2 Identification of Data Needs

The available data on the more common soluble and insoluble uranium compounds are sufficient to conclude that uranium has a low order of metallotoxicity in mammals in view of the high exposures to which humans and animals in these studies were exposed without adverse effects in many cases. Many of the nonradioactive heavy metals such as lead, arsenic, and mercury would produce very severe, perhaps fatal, injury at the levels of exposure reported for uranium in the literature (Eisenbud and Quigley 1955).

The available studies identified the kidneys as the most sensitive target of uranium's chemical toxicity, mediated by accumulation of uranium in the renal tubular epithelium to induce cellular necrosis and atrophy in the tubular wall resulting in decreased reabsorption efficiency in the renal tubules in humans (Goodman 1985; Luessenhop et al. 1958; Thun et al. 1981) and animals (Diamond et al. 1989; Rothstein 1949d; Stokinger et al. 1953). Other signs of renal tubular nephrotoxicity from chemical exposure to uranium have been demonstrated in animals (Bentley et al. 1985; Blantz 1975; De Rey et al. 1983; Diamond et al. 1989; Domingo et al. 1987; Haley et al. 1982; Kobayashi et al. 1984; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Morrow et al. 1982; Orcutt 1949; Ortega et al. 1989a; Stokinger 1981; Stokinger et al. 1953) and humans (Kathren and Moore 1986; Luessenhop et al. 1958; Thun et al. 1985; USNRC 1986; Waxweiler et al. 1981a, 1983; Zhao and Zhao 1990). The nephrotoxic effects of uranium in humans include damage to the glomerulus as evidenced by histopathological signs in the kidneys of erstwhile uranium mill workers (Thun et al. 1981). Corroborative evidence from observations in acute and intermediate exposures of rats by the oral and inhalation routes indicated that uranium exposure may also interfere with renal filtration rates by damaging the glomeruli of the kidneys of humans and animals. Histopathological examination following oral, inhalation, or parenteral exposure revealed a thickened glomerular capsular wall, shrinkage of the glomerular capillary network, lesions, and decreased glomerular

filtration rates (Avasthi et al. 1980; Blantz 1975; Dygert 1949d; Haley 1982; Kobayashi et al. 1984; Pelayo et al. 1983; Rothstein 1949c, 1949d).

Animal studies designed to examine the combined effects on the kidney of uranium and other heavy metal nephrotoxicants (lead, cadmium) would also be useful to determine whether effects are less than expected on the basis of individual toxicity, additive or synergistic. It is possible at some waste sites that multiple exposures to these metals could occur in humans.

A mechanism involving bicarbonate activity in the kidneys has been proposed for uranium-induced renal toxicity. Uranium is usually combined with either bicarbonate or a plasma protein in the blood. It has been suggested that in the kidneys, uranium is released from bicarbonate to form complexes with phosphate ligands and proteins in the tubular wall, thereby causing damage. Brady et al. (1989) proposed an alternative mechanism by which uranium exerts its renal toxicity through the inhibition of both sodium transport-dependent and -independent ATP utilization and mitochondrial oxidative phosphorylation in the renal proximal tubule. Further animal studies specifically designed to study the potential role of the inhibition of ion and nutrient transport across membranes by the uranyl ion and the effect of this phenomenon on cell death would be conducive to a more comprehensive understanding of the renal toxicity of uranium.

Although not specific to uranium toxicity, urinary catalase as an indicator of renal damage (Luessenhop et al. 1958) could be used in conjunction with other signs of renal tubular dysfunction, including mild proteinuria, aminoaciduria, and clearance of β_2-microglobulin relative to that of creatinine, as a battery of indicators of biomarkers of exposure to uranium (Limson-Zamora et al. 1996; Saccomanno et al. 1982; Thun et al. 1985). Animal studies designed to evaluate the relative sensitivities of urinary catalase and serum β_2-microglobulin as biomarkers of effect for uranium exposure would be useful in the diagnosis of human uranium exposure.

Although natural uranium has a low specific-activity of 0.67 µCi/g (25,000 Bq/g) and depleted uranium has even less (0.36 µCi/g) (10 CFR 20; Wrenn et al. 1987), it is reasonable to believe that uranium, such as highly enriched uranium with its high specific activity, may present a radiological hazard, especially in cases of human exposure (Kirk 1980; USNRC 1989). Three accidental exposure reports and health data from several years of follow-up studies are available (Kathren and Moore 1986; USNRC 1986; Zhao and

Zhao 1990). Similarly, a report from a study in which terminally ill cancer patients were injected with tetravalent and hexavalent uranium is available (Bernard and Struxness 1957). Several other human studies (Archer et al. 1973a, 1973b; Auerbach et al. 1978; Band et al. 1980; Chovil and Chir 1981; Cookfair et al. 1983; Cragle et al. 1988; Gottlieb and Husen 1982; Grace et al. 1980; Kusiak et al. 1993; Land et al. 1993; Lundin et al. 1969; Polednak and Frome 1981; Priest et al. 1982; Reyes et al. 1984; Saccomanno et al. 1971, 1976, 1982, 1988; Samet et al. 1984, 1986; Sanders 1986; Sullivan 1980a; Waxweiler et al. 1983; Whittemore and McMillan 1983; Wrenn and Singh 1983) as well as long-term animal studies with both natural and enriched uranium (Cross et al. 1981b; Filippova et al. 1978; Leach et al. 1970, 1973, 1984; Maynard and Hodge 1949; Maynard et al. 1953; Mays et al. 1985; Spiegl 1949; Stokinger et al. 1953; Tannenbaum et al. 1951) in which cancer end points were evaluated are also available. The existing studies do not show evidence of the potential radiotoxicity of uranium isotopes, particularly high specific-activity enriched uranium. Such studies in animals will be useful in a more accurate evaluation of the hazard associated with human exposure to the radiation of uranium isotopes.

Acute-Duration Exposure. Human fatalities from acute accidental exposure to airborne uranium hexafluoride have been reported, although the deaths were attributed to the sheer force of the explosions in the accident and the highly toxic hydrofluoric acid generated from the spontaneous decomposition of uranium hexafluoride upon contact with atmospheric moisture (Kathren and Moore 1986; Moore and Kathren 1985; USNRC 1986). Two poisoning incidents, an inhalation exposure to powdered uranium tetrafluoride (Zhao and Zhao 1990), and an intentional ingestion of approximately 131 mg U/kg as uranyl acetate (Pavlakis et al. 1996) resulted in renal toxicity. Follow-up studies are normally carried out in the case of industrial accidents; this should also be done in acute ingestion cases. Periodic analysis of urine for uranium over several years would be particularly valuable for the refinement of pharmacokinetic models for use in risk assessment. Acute-duration studies in animals mainly examined lethality. Inhalation acute-duration lethality studies in rats and guinea pigs are available for uranium hexafluoride (Leach et al. 1984; Spiegl 1949); oral acute-duration lethality data are available for rats and rabbits (Domingo et al. 1987; Maynard and Hodge 1949; Orcutt 1949); and dermal acute-duration lethality studies in rats, mice, guinea pigs, and rabbits (De Rey et al. 1983; Orcutt 1949) are available. Acute-duration studies which define threshold values for renal toxicity by the inhalation and oral route would be useful for assessment of brief exposures. Dermal exposure to uranium-contaminated soil is also possible. While dermal exposure to purified uranium compounds can cause toxicity in animals (De Rey et al. 1983; Orcutt 1949), the need for

further dermal studies should be assessed after information is obtained on the bioavailability of uranium from uranium-contaminated soil.

Additional research regarding the health effects of acute-duration inhalation exposure to uranium would be useful; these studies should include toxicological end points, lung doses, and metabolic fate.

Intermediate-Duration Exposure. No studies are available describing the effects of intermediate-duration exposure to uranium in humans for any route. However, an extensive animal database for this duration for all routes demonstrates that renal toxicity is a concern for intermediate-duration human exposure. The animal database for intermediate-duration inhalation exposure is essentially complete (Dygert 1949a, 1949b, 1949d; Roberts 1949; Rothstein 1949a, 1949b, 1949c; Spiegl 1949; Stokinger et al. 1953). Threshold values from these studies were used to derive inhalation MRLs for this duration (See Section 2.5 and Appendix A). The animal database for intermediate-duration oral exposure is less extensive in terms of species and compounds examined. Comprehensive studies are available for the effects of uranyl nitrate in rats and rabbits (Gilman et al. 1998a, 1998b, 1998c). The severity of histopathological alterations in the kidney increased with dose, although tests of kidney function (dye clearance, urinalysis) were normal in all dosed groups. Additionally, histopathological effects were seen in the lower dose groups without a significant increase in kidney uranium content over controls. No threshold for the histopathological effects was observed; the lowest dose tested (0.05 mg U/kg/day) was considered a minimal effect and was used to derive an oral MRL for this duration (See Section 2.5 and Appendix A). Further studies are needed to elucidate the time-course of the development of these histopathological effects; in rats, these changes were seen after 91 days, but not at 28 days. Dermal exposure to uranium-contaminated soil is also possible. While dermal exposure to purified uranium compounds can cause toxicity in animals (De Rey et al. 1983; Orcutt 1949), the need for further dermal studies should be assessed after information is obtained on the bioavailability of uranium from uranium-contaminated soil.

Chronic-Duration Exposure and Cancer. A number of epidemiological studies are available for workers exposed to uranium (miners, millers, processors). Studies that reported death from lung cancers from occupational inhalation exposure of mine workers are available (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984, 1986). Available studies document no lung cancers solely from inhaled uranium-bearing dust. It is generally accepted that lung cancers developed subsequent to inhalation of uranium-containing dusts were principally due to radon daughters and long-term cigarette

smoking, and not due to uranium metallotoxicity or uranium radioactive emissions. Existing epidemiologic studies that reported lung cancers in uranium miners, millers, and processors are inadequate for use in assessing the carcinogenic potential of uranium because the subjects were also concurrently exposed to other potential carcinogens such as radon progeny and thorium (Archer et al. 1973a; Auerbach et al. 1978; Cookfair et al. 1983; Howe et al. 1986; Polednak et al. 1982; Saccomanno et al. 1971, 1976, 1988; Samet et al. 1986; Wrenn and Singh 1983). The negative findings in most studies regarding renal injury among uranium-processing workers exposed to dusts of both soluble and insoluble uranium compounds are particularly significant in view of the high levels of exposure also reported (Eisenbud and Quigley 1955). Perhaps more sensitive indicators of renal damage, such as altered urinary amino acid, catalase, and phosphatase activities (Dygert 1949a; Stokinger et al. 1953), or the recently developed multiparametric simultaneous analysis of urinary glucose, alkaline phosphatase, and β_2-microglobulin, which may be more specific to proximal tubular damage (Limson-Zamora et al. 1996), should be used to evaluate the subjects in future studies. In addition, data from human (Russell et al. 1996) and animal studies indicate that any actual renal damage by sublethal doses was overcome and obscured by regeneration of the tubular epithelium, especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a, 1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Such repair, once completed, is histologically indistinguishable from undamaged kidney tissue. Therefore, future studies should examine newly employed miners, millers, and processors to detect potential renal effects before the process of repair occurs. The available studies have linked respiratory diseases, fatal in some cases, in uranium miners to exposure to dust-containing uranium (and other noxious substances) (Waxweiler et al. 1981a). In several of these studies, the investigators concluded that, although uranium mining may elevate the risk for nonmalignant respiratory disease, the etiology of the excess risk is not clearly identifiable because the miners were also concurrently exposed to known potent respiratory tract irritants such as diverse inhalable dust particles, silica, nickel oxide, cobalt oxide, and vanadium pentaoxide (Waxweiler et al. 1983).

Genotoxicity. Very little information on the genotoxic effects of uranium in humans (Hu and Zhu 1990; Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and in *in vitro* studies (Fajgelj et al. 1992; Lin et al. 1993) is available. Although the BEIR III (1980) and BEIR IV (1988) reports have summarized the general genotoxic effects of high-LET radiation such as might be expected from uranium, this information is not specific to uranium. Therefore, a battery of genotoxic studies with uranium compounds (including

the Ames test and tests for chromosomal damage) are needed to determine the potential of uranium to cause genetic aberrations in humans.

Reproductive Toxicity. Existing human data from uranium miners, millers, and processors (Muller et al. 1967; Waxweiler et al. 1981b; Wiese 1981) and some data from animals (Leach et al. 1970; Llobet et al. 1991; Paternain et al. 1989) indicate that uranium does not cause reproductive effects. However, other studies have reported reproductive abnormalities manifested as reduced implantations and increased fetal resorptions and dead fetuses (Paternain et al. 1989), maternal toxicity (reduced weight gain and food consumption [identified in other studies as taste aversion and not toxicity], and increased relative liver weight) and fetal toxicity (Domingo et al. 1989a), testicular lesions and degeneration and decreased testes weight (Malenchenko et al. 1978; Maynard et al. 1953), and reduced litter size (Maynard et al. 1953) following oral exposure to uranium compounds. The last three studies used high levels of orally administered uranyl nitrate, which is often considered to be the most toxic compound; the remaining positive indications are associated with relatively low oral levels of uranyl acetate(Domingo et al. 1987; Lloglet et al. 1991; Paternain et al. 1989). In dermal studies, however, uranyl acetate appears to be more toxic than uranyl nitrate for death from acute duration exposure, which is the only comparable end point for these compounds. Additional testing is needed to validate the relative toxicities of the acetate and nitrate in reproductivity studies, and then to exploit the acetate to assess other end point toxicities.

Developmental Toxicity. Because uranium can cross the placenta into the fetus, it is possible that uranium may have adverse effects on fetal development, especially metallotoxicity to the embryonic kidneys or the brain (Domingo et al. 1989a, 1989b; Paternain et al. 1989). The potential for teratogenicity and general developmental toxicity of uranium was demonstrated by results from oral animal studies in which the following were reported in mice: increased fetal mortality, reduced survivability, reduced growth (Paternain et al. 1989), reduced fetal body weight and length, an increased incidence of stunted fetuses, increased external and skeletal malformations and developmental variations, an increased incidence of cleft palate, underdeveloped renal papillae, and bipartite sternebrae, reduced or delayed ossification of the hind limb, fore limb, skull, and tail, an increase in the relative brain weight of the offspring, a reduced viability and lactation index (Domingo et al. 1989a), and embryotoxicity (Paternain et al. 1989). These effects have not been observed or documented in any human study.

Further data obtained from multigenerational developmental studies are required to determine whether human fetuses are at risk.

Immunotoxicity. Epidemiologic studies that histologically evaluated the immune system structures for the effects of inhalation exposure to uranium are available (Archer et al. 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Keane and Polednak 1983; Polednak and Frome 1981; Vich and Kriklava 1970). Although these studies were not designed as immunotoxicity studies, they found no significant immunological changes in the human subjects. The available inhalation studies in animals also found no evidence of histological changes in the spleens of rats, dogs, and monkeys exposed to uranium dioxide dusts (Leach et al. 1970, 1973). Intermediate-duration exposure of rats, rabbits, guinea pigs, and dogs to dusts containing various uranium compounds for 7–12 months produced no significant histological changes in the lymph nodes, bone marrow, or spleen, and no build-up of uranium was seen in these tissues (Stokinger et al. 1953). Similarly, rats and mice exposed to oral doses of soluble or insoluble compounds of uranium for intermediate- and chronic-duration exposures suffered no immunological damage (Malenchenko et al. 1978; Maynard et al. 1953; Tannenbaum et al. 1951). No studies are available that evaluated the immunological and lymphoreticular effects in animals following acute- or intermediate-duration inhalation exposure, the oral exposure of humans for any duration, the inhalation or oral exposure of animals for acute durations, or the dermal exposure of humans and animals to uranium compounds for any duration. Additional animal studies would be useful that use current techniques to evaluate the immunological and lymphoreticular dysfunctions that may occur with exposure to uranium compounds.

Neurotoxicity. No studies were located that specifically tested neurological functions in humans or animals following inhalation, oral, or dermal exposure to uranium. Particularly lacking in the available reports are neuropathological indicators such as narcosis or ataxia (Brown and Bloom 1987; Carpenter et al. 1988; Cragle et al. 1988; Hadjimichael et al. 1983; Kathren and Moore 1986; Polednak and Frome 1981; Reyes et al. 1984; USNRC 1986). However, the available acute-duration oral studies in rats reported dose-response neurological symptoms (piloerection, tremors, hypothermia, pupillary size decrease, exophthalmos) (Domingo et al. 1987). Available intermediate-duration animal inhalation studies reported a neurological sign (instability of gait) in dogs and cats (Dygert 1949a). Anorexia observed in another 30-day study with dogs given inhalation doses of 9.5 mg U/m^3 as uranyl nitrate hexahydrate may also have had its origin in neurological dysfunction (Roberts 1949). Similarly, cats given inhalation exposures at 18 mg U/m^3 as uranium tetrafluoride exhibited unsteady gait on the seventh day in a 30-day study (Dygert

1949a). Available chronic-duration oral data in dogs and cats also reported similar neuropathological signs (weakness and lassitude) (Rothstein 1949a). Likewise, an available acute-duration dermal exposure study in rats reported neurological signs (irritability, hyperactivity, upset equilibrium, rigidity of limbs, and respiratory arrest) (Orcutt 1949). Consequently, sensitive animal neurological battery studies of the inhalation and oral routes will be useful in evaluating and quantifying the potential for uranium to damage the nervous system in humans.

Epidemiologic and Human Dosimetry Studies. Epidemiologic studies of uranium miners, millers, and processors are available on the health effects from exposure to airborne uranium and radon daughters (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Cragle et al. 1988; Gottlieb and Husen 1982; Hadjimichael et al. 1983; Lundin et al. 1969; Polednak and Frome 1981; Samet et al. 1984, 1986; Scott et al. 1972; Waxweiler et al. 1983). However, some of the studies of miners and millers contain confounding factors and lack adequate quantitative exposure information compared with the studies of processors, which had fewer confounders and clearly identified an absence of toxic effects such as cancer. New studies that account for these confounding factors, such as effects of inhalable dust particles other than uranium, other sources of ionizing radiation, and other potentially pulmonary-toxic substances to which these workers are concurrently exposed, and that provide a more accurate measurement of the airborne concentrations of uranium to which these workers are exposed would be useful. Some of these studies also reported indications of kidney damage in these workers (Saccomanno et al. 1982; Thun et al. 1985). However, most of these studies either found no renal effects or failed to report renal effects in the subjects studied (Archer et al. 1973a, 1973b; Brown and Bloom 1987; Checkoway et al. 1988; Polednak and Frome 1981). The negative findings regarding renal injury among workers exposed to insoluble compounds may be particularly significant in view of the high levels of exposure reported (Eisenbud and Quigley 1955). Additional research regarding the health effects of acute-duration inhalation exposure to depleted uranium would be useful. This should include toxicological end points, lung doses, metabolic fate, and techniques to detect and monitor lung exposures. Also, simple and accurate monitoring methods should be developed for workers which would determine the relationship among atmospheric concentration, particle size, distribution, physical properties of the uranium aerosol, body burden, and excretion rates and pathways.

Absorption, Distribution, Metabolism, and Excretion. Information is needed on the comparative absorption of uranium compounds by the oral route, along with an assessment of its clearance from the skeleton. Quantitative data on the bioavailability of uranium from contaminated soil by the oral and dermal routes are also necessary to assess the risk of uranium-contaminated soil at hazardous waste sites.

Comparative Toxicokinetics. Numerous species (mice, rats, rabbits, guinea pigs, dogs, and monkeys) have been tested for their response to inhaled or ingested uranium. The results from these studies clearly demonstrate that there is a considerable difference in toxic responses among species. For example, rabbits appear to be unusually susceptible to the lethal effects of uranium (Maynard and Hodge 1949; Orcutt 1949; Stokinger et al. 1953); whereas dogs developed glandular neoplasms of the lungs (Leach et al. 1973), a type of lung cancer that is not observed in humans; and guinea pigs required far greater air concentrations (15x) for 2-minute exposures than did rats to produce an effect (Leach et al. 1984).

Methods for Reducing Toxic Effects. Uranium forms complexes with the bicarbonate ion (Cooper et al. 1982) and has been administered prophylactically after uranium exposure (Fisher et al. 1991). Bicarbonate can alkalize the blood to a degree that facilitates the excretion of uranium via the kidneys. This in turn, can prevent uptake by and deposition in critical tissues (kidney, bone). Chelation has been tested in animals and found to have a limited potential, though possibly valuable, role in reducing acute uranium toxicity. Further research is needed to validate, refute, or refine method(s) for reducing the toxic effects of uranium compounds. No verified methods for reducing the toxic effects of long-term exposure to uranium are currently available.

Children's Susceptibility. Specific information is not available on whether children are more susceptible than adults to the effects of uranium. No reports were located describing toxicity in children as the result of uranium exposure. It is probable, however, that if exposure levels were high enough, signs of renal toxicity would be observed similar to that seen in adults exposed accidentally (Zhao and Zhao 1990) or intentionally (Pavlaikis 1996). Data needs relating to development, both pre-natal and post-natal, are discussed in the previous section on Developmental Toxicity.

A study by the oral route establishing a threshold for renal effects in weanling and adult rats of the same strain is needed to determine if susceptibility to uranium toxicity varies with age. Histopathological studies

and urinalysis should be performed, as well as measurement of uranium in excreta for both groups. At termination in this study, uranium content should be measured in tissues, particularly bone and kidney. This will provide information on whether retention of uranium in bone is age-dependent (as assumed by analogy with calcium in PBPK models) and on whether kidney burden associated with uranium toxicity is age-related.

More information is needed on the absorption of various forms of uranium in young animals. Also, studies are needed on whether maternally stored bone uranium is mobilized to blood during pregnancy and lactation and whether this can increase exposure to the fetus and neonate. Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

A number of studies currently being conducted on the toxicity of uranium were found in the Federal Research in Progress database (FEDRIP 1999). Selected studies are listed in Table 2-11.

Table 2-11. Ongoing Studies on Health Effects of Uranium

Investigator	Affiliation	Study	Funding agency
Kathren RL	Washington State University Health Research and Education Center, Richland WA	United States transuranium and uranium registries	DOE
Saccomanno G	Saint Mary's Hospital And Medical Center, Dept of Cytopathology, Grand Junction CO	Early lung cancer detection in uranium miners with abnormal sputum cytology	DOE
Gilland, Frank	Univ of New Mexico, Albuquerque NM	Uranium miners health study	NIH, National Center for Research Resources
Sandler DP	NIEHS, NIH, Research Triangle Park NC	Cancer risk in Czech uranium miners	NIEHS
Belinsky SA	Lovelace Biomedical and Environmental Research, Albuquerque NM	Tumor suppressor gene methylation in lung adenocarcinoma	NIEHS
Spiegleman D	Harvard School of Public Health, Boston MA	Measurement error in occupational cohort studies	NCI
Saffiotti U	NCI, NIH, Bethesda MD	Respiratory carcinogenesis by chemical and physical factors	NCI, Division of Basic Sciences
Crowell R	Department of Veterans Affairs Medical Center, Albuquerque NM	Lung cancer in uranium miners: a tissue resource	Department of Veterans Affairs Research and Development
Walsh M	Department of Veterans Affairs Medical Center, Boston MA	Follow-up and monitoring of gulf war veterans with fragments of depleted uranium and other sources of depleted uranium.	Department of Veterans Affairs Research and Development
Keogh J	Department of Veterans Affairs Medical Center, Baltimore, MD	Assessment of depleted uranium exposure during the persian gulf war.	Department of Veterans Affairs Research and Development
Standiford H	Department of Veterans Affairs Medical Center, Baltimore, MD	Evaluation of gulf war veterans to determine health effects of depleted uranium.	Department of Veterans Affairs Research and Development
McDiarmid M	University of Maryland School of Medicine, Baltimore, MD	Health effects of depleted uranium in Gulf War veterans	Department of Veterans Affairs Research and Development
McClain D	Armed Forces Radiobiology Research Institute, Bethesda MD	Health Effects of Embedded Depleted Uranium	United States Department of Defense
(supervising scientist)	University of Sydney, Sydney, Australia	Uranium measurement in occupationally exposed mill workers	Commonwealth Institute of Health, Australia

DOE = Department of Energy; NCI = National Cancer Institute; NIEHS = National Institutes of Environmental Health Sciences; NIH = National Institute of Health

Source: FEDRIP 1999 and http://www.afrri.usuhs.mil/www/research/teams/teamdu.html