3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

The health effects associated with oral or dermal exposure to natural and depleted uranium appear to be primarily chemical in nature and not radiological, while those from inhalation exposure may also include a slight radiological component, especially if the exposure involves prolonged exposure to insoluble uranium compounds. 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 rays 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 is naturally occurring or has been produced in nuclear reactors and in high energy physics experiments. It exists in a number of isotopic forms (NNDC 2011), 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 (or bismuth in the case of ^{233}U). The radionuclides in these transformation series (such as isotopes of radium and radon), emit alpha or beta particles, as well as gamma and x-rays, with energies and intensities that are unique to the individual radionuclide.

There are three basic categories of uranium isotope mixtures (based on the mass percentage of ^{235}U relative to that of the earth's crust): natural uranium, enriched uranium, and depleted uranium. Natural uranium in the earth's crust is comprised of 99.2742% ^{238}U, 0.7204% ^{235}U, and 0.0054% ^{234}U by mass. Combining these mass percentages with the unique half-life of each isotope converts mass into radioactivity units and shows that crustal uranium contains 48.7% ^{234}U, 2.27% ^{235}U, and 49.0% ^{238}U by radioactivity, and has a very low specific activity of 0.69 μCi/g based on data compiled by the National Nuclear Data Center (NNDC 2011). Natural uranium in the environment can vary somewhat from these ratios due to physical and environmental factors, as shown by the varying ratios of natural uranium in air (EPA 2008). 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 mass 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," which possesses even less radioactivity (0.36 μCi/g) than natural uranium. The USNRC 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," although depleted uranium is specified when this use benefits the text. 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.

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, uranium hexafluoride, uranyl fluoride, uranium tetrachloride) were the most potent systemic toxicants. The poorly water-soluble compounds (uranium tetrafluoride, sodium diuranate, ammonium diuranate) were of moderate-to-low systemic toxicity, and the insoluble compounds (uranium trioxide, uranium dioxide, uranium peroxide, triuranium octaoxide) had a much lower potential to cause systemic toxicity but could cause pulmonary toxicity when exposure was by inhalation. *The terms soluble, poorly soluble, and insoluble are often used in this profile without relisting the specific compounds.* Generally, hexavalent uranium, which tends to form relatively soluble compounds, is more likely to be a systemic toxicant than tetravalent uranium, which forms relatively insoluble compounds. Ingested uranium is less toxic than inhaled uranium, which may be partly attributable to the relatively low gastrointestinal absorption of uranium compounds.

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 combined ^{234}U and ^{235}U in enriched uranium), 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. Although the mechanism of this interaction is as yet unclear, it is not necessary to know it in order to identify critical targets of toxicity or evaluate the dose-response relationships.

3.2 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, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

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.

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 (LOAELs) 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 the general public alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of uranium are indicated in Table 3-1 and Figure 3-1.

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.

3.2.1 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 et al. 1951). A study summary of the data for inhalation toxicity (lethality) studies in mice exposed to equivalent

[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 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 et al. 1951). Although uranium tetrachloride is highly soluble in water, it is easily hydrolyzed and oxidized into less soluble uranyl chloride and insoluble 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.

3.2.1.1 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, most likely due to the resulting exposure to hydrogen fluoride. 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. 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 was not evaluated in some of the studies (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984a, 1986); additionally, the contributions of crystalline silica and diesel engine exhaust to the cancer rate ascribed to radon have not been evaluated. 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 significant increase in overall deaths attributable to exposure to uranium (Archer et al. 1973b; Boice et al. 2008; Checkoway et al. 1988; Cragle et al. 1988; Hadjimichael et al.

1983; NIOSH 1987; Pinkerton et al. 2004; Polednak and Frome 1981; Scott et al. 1972; Waxweiler et al. 1983). Results of several mortality assessments of populations living near uranium mining and milling operations have not demonstrated significant associations between mortality and exposure to uranium (Boice et al. 2003, 2007a, 2007b, 2010).

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[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. 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). For both accidents, the observed effects are suggestive that inhalation of hydrofluoric acid was responsible for death.

A study of U.K. Gulf War veterans (>50,000 veterans) did not find a significant increase in the risk of dying in a 13-year follow-up period, as compared to >50,000 veterans not deployed to the Gulf. Among the 7% of Gulf War veterans who self reported exposure to depleted uranium, a non-statistically significant increase in the risk of disease-related deaths was found (mortality rate ratio of 1.99, 95% confidence interval [CI] of 0.98–4.04) (Macfarlane et al. 2005).

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. The 2-minute LC_{50} values (95% CIs) for the rats and guinea pigs were 120,290 mg U/m^3 (99,270–145,750 mg U/m^3) and 62,080 mg U/m^3 (43,380–88,830 mg U/m^3), respectively. For a 5-minute inhalation exposure, the LC_{50} in rats was estimated as 38,600 mg U/m^3 (26,760–55,720 mg U/m^3); the LC_{50} for a 10-minute inhalation was estimated as 12,010 mg U/m^3 (10,090–14,290 mg U/m^3).

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

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/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/day, 5 days/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/day, 5.5 days/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 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/day, 5 days/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 of the dogs tested (Dygert 1949d). Inhalation of air containing 15 mg U/m^3 (as sodium diuranate) for 6 hours/day, 5.5 days/week for 5 weeks caused 13 and 28% mortality in guinea pigs and rabbits, respectively (Rothermel 1949).

Insoluble uranium compounds were also lethal to animals by the inhalation route, but at higher concentrations than soluble compounds. Exposure to 15.8 mg U/m^3 (as uranium trioxide) 6 hours/day, 5.5 days/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/day, 5.5 days/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/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/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/day, 5.5 days/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). Out of 25 exposed dogs, 1 dog died at 0.25 mg U/m^3 and another died at 2 mg U/m^3. Death may or may not have been attributable to uranium, according to the study investigators.

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 3-1 and plotted in Figure 3-1.

3.2.1.2 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.

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Long- Evans)	5 min				18210 M (40% mortality by day 14 postexposure)	Leach et al. 1984 Uranium Hexafluoride	
2	Rat (NS)	1 d 10 min				1544 (75% mortality 30 days postexposure)	Spiegl 1949 Uranium Hexafluoride	
3	Mouse (NS)	1 d 10 min				637 (20% mortality 30 days post-exposure)	Spiegl 1949 Uranium Hexafluoride	
4	Gn Pig (Hartley)	2 min				23040 M (2/6 died 48 hrs postexposure)	Leach et al. 1984 Uranium Hexafluoride	
5	Gn Pig (NS)	1 d 10 min				637 (13% mortality 30 days post-exposure)	Spiegl 1949 Uranium Hexafluoride	
Systemic								
6	Rat (Long- Evans)	5 min	Resp		9131	54503 M (severe nasal congestion, hemorrhage)	Leach et al. 1984 Uranium Hexafluoride	
			Renal		392 M (glucosuria)			
7	Rat (Long- Evans)	10 min	Renal		426 M (proteinuria, glucosuria, and polyuria)		Leach et al. 1984 Uranium Hexafluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
8	Rat (Long- Evans)	2 min	Renal	920 M	1430 M (proteinuria)		Leach et al. 1984 Uranium Hexafluoride	
9	Rat (Fischer- 344)	once 100 min	Resp			5051 M (severe alveolar fibrosis)	Morris et al. 1990 Uranium Dioxide	
10	Rat (NS)	1 d 10 min	Resp			637 (gasping in 100% of rats; severe irritation of nasal passages)	Spiegl 1949 Uranium Hexafluoride	
			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 Uranium Hexafluoride	
			Ocular		637 (conjunctivitis)			
12	Gn Pig (Hartley)	2 min	Renal		23040 M (glucosuria and polyuria)		Leach et al. 1984 Uranium Hexafluoride	
13	Gn Pig (Hartley)	2 min	Renal		23040 M (glucosuria and polyuria)		Leach et al. 1984 Uranium Hexafluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
14	Dog [Beagle]	once 0.5-1 hr	Resp	270			Morrow et al. 1982a Uranyl Fluoride	
			Renal			250 (extensive degeneration in kidney cortex and tubules)		
Immuno/ Lymphoret								
15	Rat (Fischer- 344)	once			44 M (increased macrophage activity)		Morris et al. 1989 Uranium Dioxide	
16	Rat (Fischer- 344)	once			132 M (increased macrophage activity)		Morris et al. 1992 Uranium Dioxide	
INTERMEDIATE EXPOSURE								
Death								
17	Rat (NS)	30 d 6 hr/d				18 (32% mortality)	Dygert 1949a Uranium Tetrafluoride	
18	Rat (NS)	30 d 6 hr/d				13.3 (75% mortality)	Spiegl 1949 Uranium Hexafluoride	
19	Mouse (NS)	23 d 5 d/wk 5 hr/d				15.4 (63% mortality)	Dygert 1949d Uranium Peroxide	
20	Mouse (NS)	30 d 6 hr/d				2 (92% mortality)	Spiegl 1949 Uranium Hexafluoride	
21	Gn Pig (NS)	30 d 6 hr/d				18 (15% mortality)	Dygert 1949a Uranium Tetrafluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
22	Gn Pig (NS)	30 d 6 hr/d				6.8 (20% mortality)	Dygert 1949b Ammonium Diuranate	
23	Gn Pig (NS)	23 d 5 d/wk 5 hr/d				15.4 (40% mortality)	Dygert 1949d Uranium Peroxide	
24	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d				9.2 (55% mortality)	Rothstein 1949a Uranyl Fluoride	
25	Gn Pig (NS)	5 wk 5.5 d/wk 6 hr/d				15 (13% mortality)	Rothstein 1949d Sodium Uranate	
26	Gn Pig (NS)	30 d 6 hr/d				13.3 (45% mortality)	Spiegl 1949 Uranium Hexafluoride	
27	Dog (NS)	30 d 6 hr/d				18 (lethal dose)	Dygert 1949a Uranium Tetrafluoride	
28	Dog (NS)	30 d Cont.				9.5 (75% mortality)	Roberts 1949 Uranyl Nitrate	
29	Dog (NS)	4 wk 6 d/wk 6 hr/d				15.8 (17% mortality)	Rothstein 1949c Uranium Trioxide	
30	Dog (NS)	5 wk 6 d/wk 6 hr/d				9.2 (100% mortality)	Rothstein 1949a Uranyl Fluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
31	Dog (NS)	30 d 6 hr/d				13.3 (40% mortality)	Spiegl 1949 Uranium Hexafluoride	
32	Rabbit (NS)	30 d 6 hr/d				18 (33% mortality)	Dygert 1949a Uranium Tetrafluoride	
33	Rabbit (NS)	30 d 6 hr/d				6.8 (100% mortality)	Dygert 1949b Ammonium Diuranate	
34	Rabbit (NS)	23 d 5 hr/d 5 d/wk				15.4 (80% mortality)	Dygert 1949d Uranium Peroxide	
35	Rabbit (NS)	4 wk 6 d/wk 6 hr/d				15.8 (67% mortality)	Rothstein 1949c Uranium Trioxide	
36	Rabbit (NS)	5 wk 6 d/wk				19.4 (60% mortality)	Rothstein 1949b Uranium Dioxide	
37	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d				15 (28% mortality)	Rothstein 1949d Sodium Uranate	
38	Rabbit (NS)	30 d 6 hr/d				2 (80% mortality)	Spiegl 1949 Uranium Hexafluoride	
39	Cat (NS)	30 d 6 hr/d				18 (100% mortality)	Dygert 1949a Uranium Tetrafluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
40	Cat (NS)	23 d 5 d/wk 5 hr/d					15.4	(100% mortality)	Dygert 1949d Uranium Peroxide	
41	Cat (NS)	30 d Cont.					2	(100% mortality)	Roberts 1949 Uranyl Nitrate	
Systemic										
42	Rat (NS)	30 d 6 hr/d	Gastro		0.4	(ulceration of cecum)			Dygert 1949a Uranium Tetrafluoride	
			Hemato	18						
			Hepatic		0.4	(focal necrosis of liver)				
			Renal	4	18	(slight azotemia)				
			Bd Wt	4			18	(26% decrease body weight)		
43	Rat (NS)	30 d 6 hr/d	Resp		6.8	(intersitial bronchopneumonia in 25% of animals; nasal irritation)			Dygert 1949b Ammonium Diuranate	
			Hemato		6.8	(decreased RBC, hemoglobin)				
			Renal		6.8	(minimal necrosis of tubular epithelium followed by regeneration)				
			Bd Wt	6.8						

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
44	Rat (NS)	30 d Cont.	Hemato	2.1	9.5	(decreased RBC, hemoglobin)	Roberts 1949 Uranyl Nitrate	
			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)		
45	Rat (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight degenerative changes in the lungs)	Rothstein 1949c Uranium Trioxide	
			Hemato		16	(increased percentage of myeloblasts and lymphoid cells of bone marrow)		
			Hepatic	16				
			Renal		16	(mild to severe tubular necrosis)		
			Bd Wt	16				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
46	Rat (NS)	5 wk 6 d/wk 6 hr/d	Hemato	9.2			Rothstein 1949a Uranyl Fluoride	
			Renal	0.5	2.2 (minimal renal tubular degeneration)			
			Bd Wt	2.2	9.2 (unspecified moderate weight loss)			
47	Rat (NS)	5 wk 6 d/wk	Resp	19.4			Rothstein 1949b Uranium Dioxide	
			Hemato	19.4				
			Renal	19.4				
48	Rat (NS)	5 wk 5.5 d/wk 6 hr/d	Hemato	15			Rothstein 1949d Sodium Uranate	
			Renal		15 (moderate renal degeneration and necrosis)			

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
49	Rat (NS)	30 d 6 hr/d	Resp	2			13.3	(lung edema, hemorrhage, emphysema)	Spiegl 1949 Uranium Hexafluoride	
			Hemato	13.3						
			Renal	0.05	0.2	(mild renal tubular damage)				
			Ocular	2	13.3	(eye irritation)				
			Bd Wt	2			13.3	(6% weight loss)		
50	Mouse (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b Uranium Dioxide	
			Hemato	19.4						
			Renal	19.4						
			Bd Wt	19.4						

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
51	Mouse (NS)	30 d 6 hr/d	Resp	2			13.3	(lung edema, hemorrhage, and emphysema; inflammation of bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 Uranium Hexafluoride	
			Renal	2			13.3	(severe renal-tubular degeneration followed by regeneration, and necrosis, and the presence of casts in the tubules)		
			Ocular	2	13.3	(eye irritation)				
			Bd Wt	2	13.3	(unspecified weight loss)				
52	Gn Pig (NS)	30 d 6 hr/d	Hemato	18					Dygert 1949a Uranium Tetrafluoride	
			Renal	4			18	(moderate to severe necrosis of corticomedullary tubular epithelium)		
53	Gn Pig (NS)	30 d Cont.	Bd Wt	2.1			9.5	(2.9-27.9% decreased body weight)	Roberts 1949 Uranyl Nitrate	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
54	Gn Pig (NS)	5 wk 6 d/wk 6 hr/d	Renal	2.2			9.2	(severe degeneration of renal tubular epithelium)	Rothstein 1949a Uranyl Fluoride	
			Bd Wt		2.2	(unspecified moderate weight loss)				
55	Gn Pig (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b Uranium Dioxide	
			Hemato	19.4						
			Renal	19.4						
			Bd Wt	19.4						
56	Gn Pig (NS)	30 d 6 hr/d	Resp	2			13.3	(lung edema, hemorrhage, and emphysema, acute inflammation was seen in the bronchi, alveoli, and alveolar interstitices)	Spiegl 1949 Uranium Hexafluoride	
			Renal	2			13.3	(severe renal-tubular degeneration, necrosis, regeneration; casts in the tubules)		
			Bd Wt	2	13.3	(13% decreased body weight)				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
57	Gn Pig	7.5 months 33 hr/wk	Renal	0.2			Stokinger et al. 1953 Uranium Tetrachloride	
			Bd Wt	0.2				
58	Gn Pig	9 mo 5.5 d/wk 6 hr/d	Renal	0.05			Stokinger et al. 1953 Uranium Hexafluoride	
			Bd Wt	0.05				
59	Gn Pig (NS)	7 mo 33 hrs/wk	Renal	10			Stokinger et al. 1953 Uranium Dioxide	
			Bd Wt	10				
60	Gn Pig (NS)	6.5 mo 33 hrs/wk	Hemato	2 M			Stokinger et al. 1953 Uranyl Nitrate	
			Renal	2 M				
61	Gn Pig	9 mo 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 Uranium Tetrafluoride	
			Renal	3				
			Bd Wt	3				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
62	Dog (NS)	30 d 6 hr/d	Gastro	4		18 (vomited blood)	Dygert 1949a Uranium Tetrafluoride	
			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)		
63	Dog (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4			Dygert 1949d Uranium Peroxide	
			Bd Wt	15.4				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
64	Dog (NS)	30 d Cont.	Resp	2.1	9.5	(rales; slight degeneration in lung epithelium)			Roberts 1949 Uranyl Nitrate	
			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						
65	Dog (NS)	4 wk 6 d/wk 6 hr/d	Resp		16	(very slight pulmonary degenerative changes)			Rothstein 1949c Uranium Trioxide	
			Hemato	16						
			Hepatic	16						
			Renal		16	(mild to severe tubular necrosis)				
			Bd Wt	16						

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
66	Dog (NS)	5 wk 6 d/wk 6 hr/d	Gastro	2.2			9.2	(vomited blood)	Rothstein 1949a Uranyl Fluoride	
			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)		
67	Dog (NS)	5 wk 6 d/wk	Resp	9.2					Rothstein 1949b Uranium Dioxide	
			Hemato	9.2						
			Renal	1.1[c]	8.2	(slight renal tubular degeneration in 2/6)				
			Bd Wt	9.2						
68	Dog (NS)	30 d 6 hr/d	Resp	0.2	2	(slight pneumonia)			Spiegl 1949 Uranium Hexafluoride	
			Hemato	2						
			Renal	0.05	0.2	(slight pneumonia)				
			Ocular	2	13.3	(conjunctivitis)				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
69	Rabbit (NS)	30 d 6 hr/d	Hemato	18			Dygert 1949a Uranium Tetrafluoride	
			Renal		0.4 (increased urinary catalase and phosphatase)			
			Bd Wt	3		18 (24% decreased body weight)		
70	Rabbit (NS)	30 d 6 hr/d	Resp			6.8 (pulmonary edema, hemorrhage, and necrosis)	Dygert 1949b Ammonium Diuranate	
			Hemato		6.8 (increased neutrophils, decreased lymphocytes)			
			Renal			6.8 (severe necrosis of the tubular epithelium)		

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
71	Rabbit (NS)	23 d 5 d/wk 5 hr/d	Resp				15.4	(edematous alveoli, alveolar hemorrhage, hyperemia, and atelectasis)	Dygert 1949d Uranium Peroxide	
			Hemato	15.4						
			Hepatic	15.4						
			Renal		15.4	(moderate corticomedullary tubule necrosis with regeneration of tubular cells; azotemia)				
			Bd Wt	15.4						
72	Rabbit (NS)	30 d Cont.	Resp	0.2					Roberts 1949 Uranyl Nitrate	
			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)				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
73	Rabbit (NS)	4 wk 6 d/wk 6 hr/d	Resp				16	(hemorrhage and consolidation in lungs of animals that died)	Rothstein 1949c Uranium Trioxide	
			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						
74	Rabbit (NS)	5 wk 6 d/wk	Resp	19.4					Rothstein 1949b Uranium Dioxide	
			Hemato	19.4						
			Renal	9.2			19.4	(severe tubular necrosis in dying animals)		
			Bd Wt	8.2	9.2	(unspecified decreased body weight)				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
75	Rabbit (NS)	5 wk 5.5 d/wk 6 hr/d	Hepatic		15 (slight decrease in lactate)		Rothstein 1949d Sodium Uranate	
			Renal		15 (progressive degeneration and necrosis followed by regeneration of tubular epithelium; increased NPN)			
			Bd Wt	15				
76	Rabbit (NS)	30 d 6 hr/d	Resp	0.2	2 (severe pulmonary edema)		Spiegl 1949 Uranium Hexafluoride	
			Hemato	13				
			Renal		0.2 (mild tubular degeneration)			
			Bd Wt	0.2	2 (12% decreased body weight)			
77	Rabbit (NS)	6.5 mo 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 Uranyl Nitrate	
			Renal		0.25 mild tubular atrophy)			
			Bd Wt			2 (weight loss)		

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
78	Rabbit	9 mo 5.5 d/wk 6 hr/d	Renal		0.2 (very mild tubular injury)		Stokinger et al. 1953 Uranium Hexafluoride	
			Bd Wt	0.2				
79	Rabbit	9 mo 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 Uranium Tetrafluoride	
			Renal	3				
			Bd Wt	3				
80	Rabbit (NS)	7 mo 33 hrs/wk	Hemato	10			Stokinger et al. 1953 Uranium Dioxide	
			Renal	10				
			Bd Wt	10				
81	Rabbit	7.5 mo 33 hr/wk	Renal	0.2			Stokinger et al. 1953 Uranium Tetrachloride	
			Bd Wt	0.2				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
82	Cat (NS)	30 d 6 hr/d	Resp		18 (rhinitis)		Dygert 1949a Uranium Tetrafluoride	
			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)			
83	Cat (NS)	23 d 5 d/wk 5 hr/d	Hemato	15.4			Dygert 1949d Uranium Peroxide	
			Renal			15.4 (azotemia)		
			Bd Wt	15.4				
84	Cat (NS)	5 wk 6 d/wk 6 hr/d	Resp	2.2	9.2 (rhinitis)		Rothstein 1949a Uranyl Fluoride	
			Gastro	2.2		9.2 (vomited blood prior to death)		
			Renal	2.2		9.2 (severe degeneration of renal tubular epithelium)		

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
85	Rat (NS)	30 d 6 hr/d			0.4 (edematous cecal lymph nodes; focal necrosis of spleen)		Dygert 1949a Uranium Tetrafluoride	
86	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 Ammonium Diuranate	
87	Rat (NS)	30 d Cont.		2.1	9.5 (decreased absolute number of lymphocytes and neutrophils)		Roberts 1949 Uranyl Nitrate	
Neurological								
88	Rat (Sprague-Dawley)	3 wk 4 d/wk 0.5 hr (NS)			190 M (increased spontaneous activity; decreased spatial working memory)		Monleau et al. 2005 Uranium Dioxide	
89	Dog (NS)	30 d 6 hr/d		4	18 (weakness and unsteady gait)		Dygert 1949a Uranium Tetrafluoride	
90	Cat (NS)	30 d 6 hr/d			18 (weakness and unsteady gait)		Dygert 1949a Uranium Tetrafluoride	

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
91	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d				5 (4.5% mortality)	Leach et al. 1970, 1973 Uranium Dioxide	
Systemic								
92	Monkey	5 yr 5 d/wk 5.4 hr/d	Resp		5.1[d] (minimal pulmonary hyaline fibrosis)		Leach et al. 1970, 1973 Uranium Dioxide	
			Hepatic	5.1				
			Renal	5.1				
			Bd Wt	5.1				
93	Rat (NS)	1 yr 33 hrs/wk	Resp	0.2			Stokinger et al. 1953 Uranium Tetrachloride	
			Gastro	0.2				
			Hepatic	0.2				
			Renal	0.05	0.2 (slight to mild tubular injury)			
			Endocr	0.2				
			Bd Wt	0.2				
94	Rat (NS)	1 yr 33 hrs/wk	Resp	2			Stokinger et al. 1953 Uranyl Nitrate	
			Renal	0.25	2 (mild to marked renal tubular atrophy)			
			Bd Wt	2				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
95	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 Uranium Hexafluoride	
			Cardio	0.2				
			Gastro	0.2				
			Hemato	0.2				
			Hepatic	0.2				
			Renal	0.05	0.2 (very mild renal tubular lesions)			
			Endocr	0.2				
			Dermal	0.2				
			Bd Wt	0.2				
96	Rat (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 Uranyl Nitrate	
			Renal		2 (mild tubular atrophy)			
			Bd Wt	2				
97	Rat (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 Uranium Tetrafluoride	
			Renal	3				
			Bd Wt	3				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
98	Rat	1 yr 33 hrs/wk	Hemato	10			Stokinger et al. 1953 Uranium Dioxide	
			Renal	10				
			Bd Wt	10				
99	Dog (Beagle)	1-5 yr 5 d/wk 5.4 hr/d	Resp		5.1 (lung fibrosis)		Leach et al. 1970, 1973 Uranium Dioxide	
			Hemato	5.1				
			Renal	5.1				
			Bd Wt	5.1				
100	Dog (NS)	1 yr 33 hrs/wk	Hemato	0.2			Stokinger et al. 1953 Uranium Tetrachloride	
			Hepatic	0.2				
			Renal	0.05[e]	0.2 (slight tubular atrophy)			
			Bd Wt	0.2				
101	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 Uranyl Nitrate	
			Hepatic	2				
			Renal	0.15	0.25 (mild to moderate tubular atrophy)			
			Bd Wt	2				

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
102	Dog	1 yr 33 hrs/wk	Hemato	10			Stokinger et al. 1953 Uranium Dioxide	
			Renal	1	10 (slight to mild tubular degeneration)			
			Bd Wt	10				
103	Dog	1 yr 5.5 d/wk 6 hr/d	Hemato	3			Stokinger et al. 1953 Uranium Tetrafluoride	
			Renal	0.5	3 (tubular damage)			
			Bd Wt	3				
104	Dog (NS)	1 yr 5.5 d/wk 6 hr/d	Resp	0.2			Stokinger et al. 1953 Uranium Hexafluoride	
			Hemato	0.2				
			Renal	0.05	0.2 (mild tubular injury)			
			Bd Wt	0.2				
105	Dog (NS)	2 yr 5.5 d/wk 6 hr/d	Hemato	2			Stokinger et al. 1953 Uranyl Nitrate	
			Renal		2 (moederate tubular atrophy)			

Table 3-1 Levels of Significant Exposure to Uranium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
106	Dog (Beagle)	5 yr 5 d/wk 5.4 hr/d			5.1 (minimal lymph node fibrosis)		Leach et al. 1970, 1973 Uranium Dioxide	
Cancer								
107	Rat (Sprague-Dawley)	65 wk 5 d/wk 4.2 hr/d				8.4 M (CEL: malignant lung tumors)	Mitchel et al. 1999 Uranium dust	
108	Dog (NS)	1-5 yr 5 d/wk 5.4 hr/d				5.1 (CEL: lung cancer)	Leach et al. 1973 Uranium Dioxide	

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.0001 mg U/m3 for soluble uranium compounds based on a LOAELADJ of 0.032 mg/m3 and an uncertainty factor of 300 (3 for used of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

c Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.002 mg U/m3 for insoluble uranium compounds based on a NOAELADJ of 0.24 mg/m3 and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

d Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.0008 mg U/m3 for insoluble uranium compounds based on a LOAELADJ of 0.82 mg/m3 and an uncertainty factor of 1000 (10 for use of LOAEL, 10 for extrapolation from animals to humans and 10 for human variability).

e Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.00004 mg U/m3 for soluble uranium compounds based on a BMCLADJ of 0.0037 mg/m3 and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation

Acute (≤14 days)

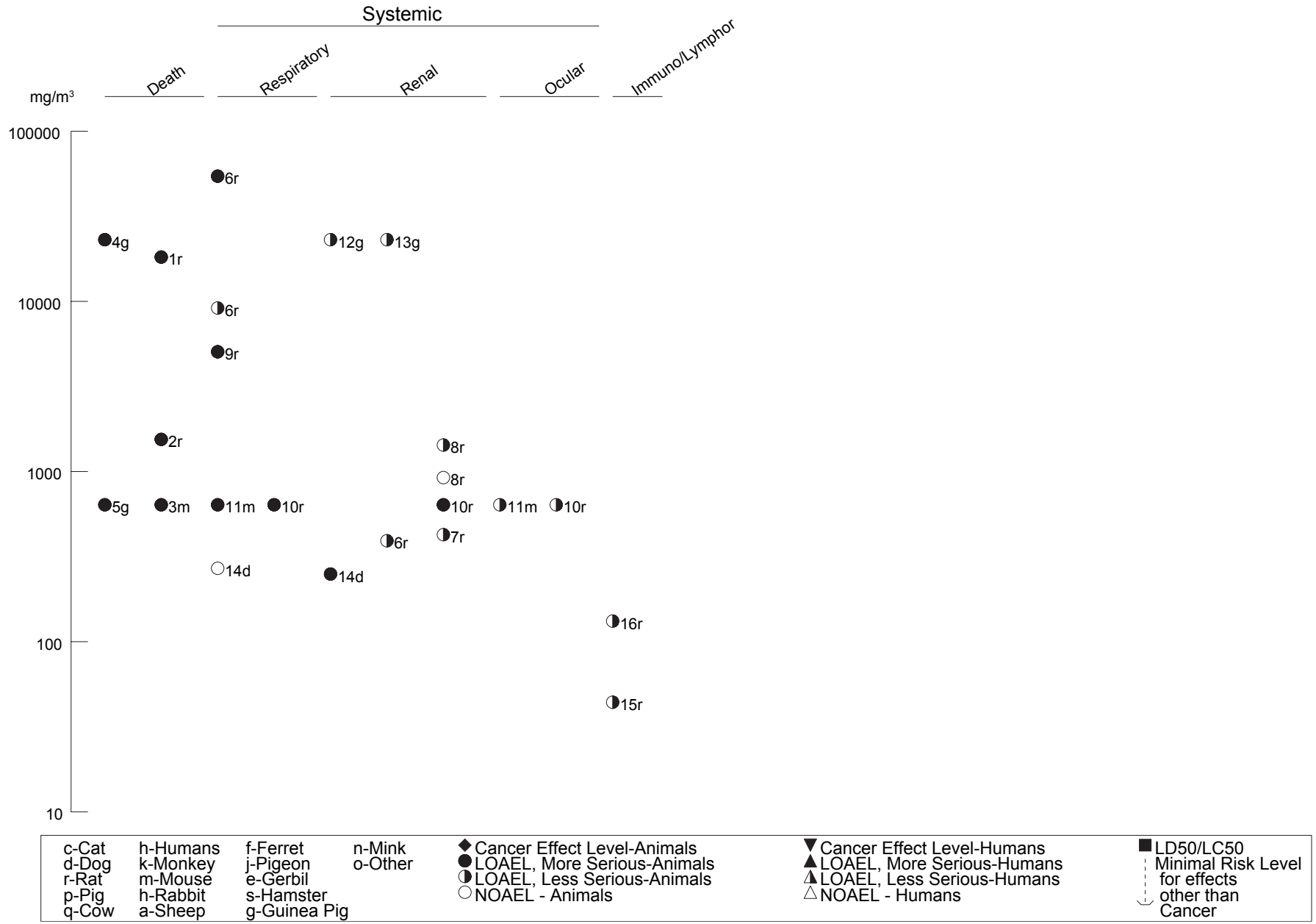


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Intermediate (15-364 days)

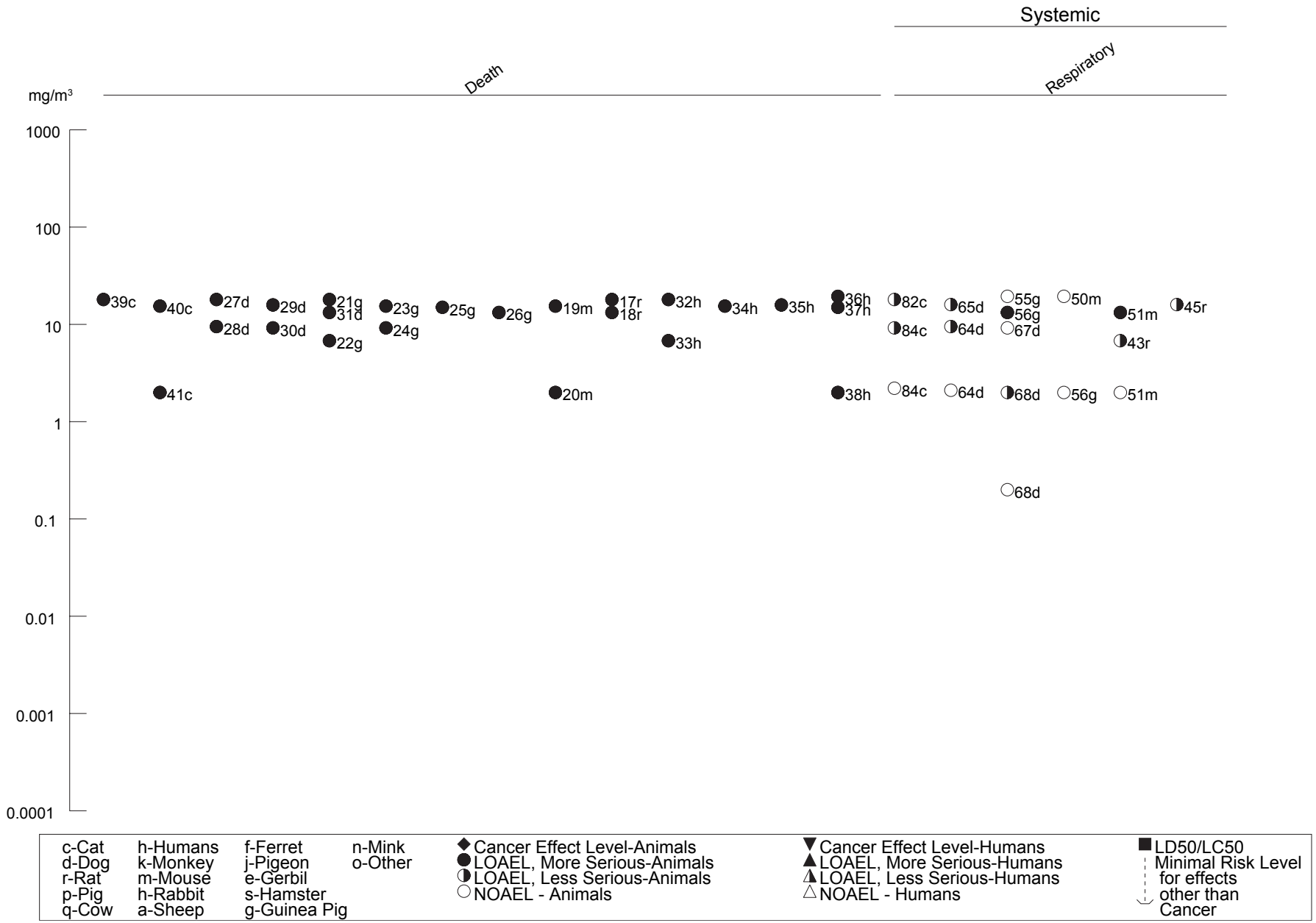


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Intermediate (15-364 days)

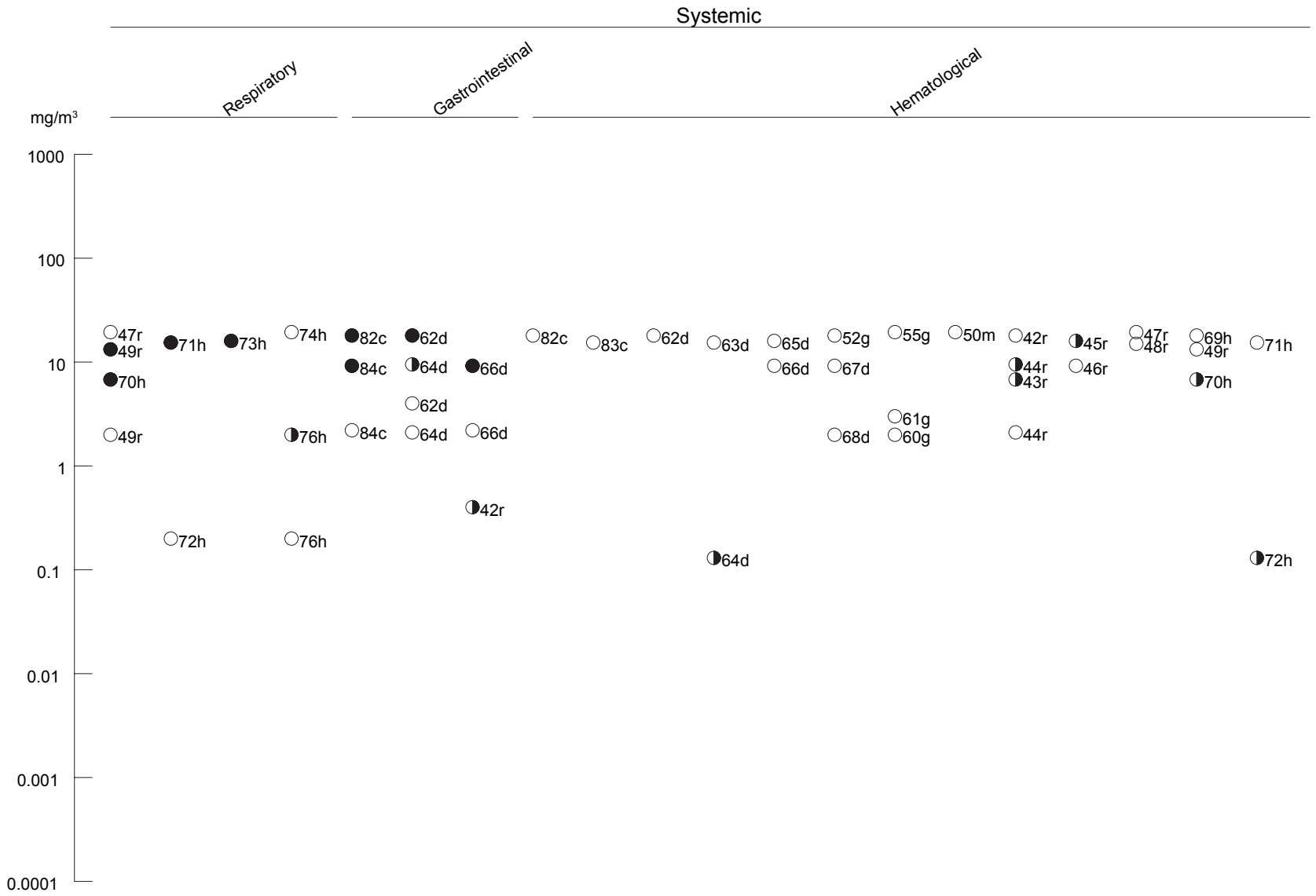


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Intermediate (15-364 days)

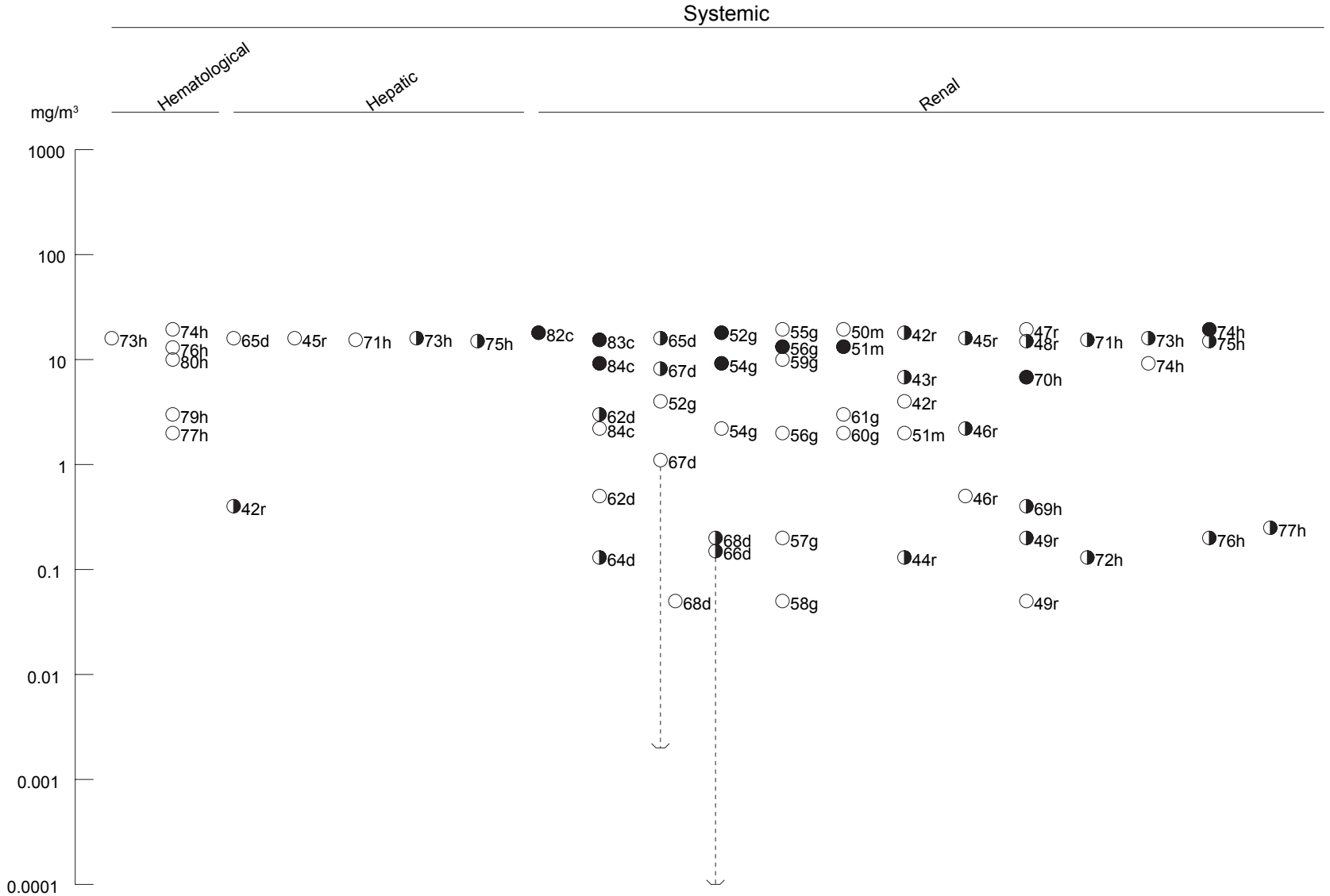


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Intermediate (15-364 days)

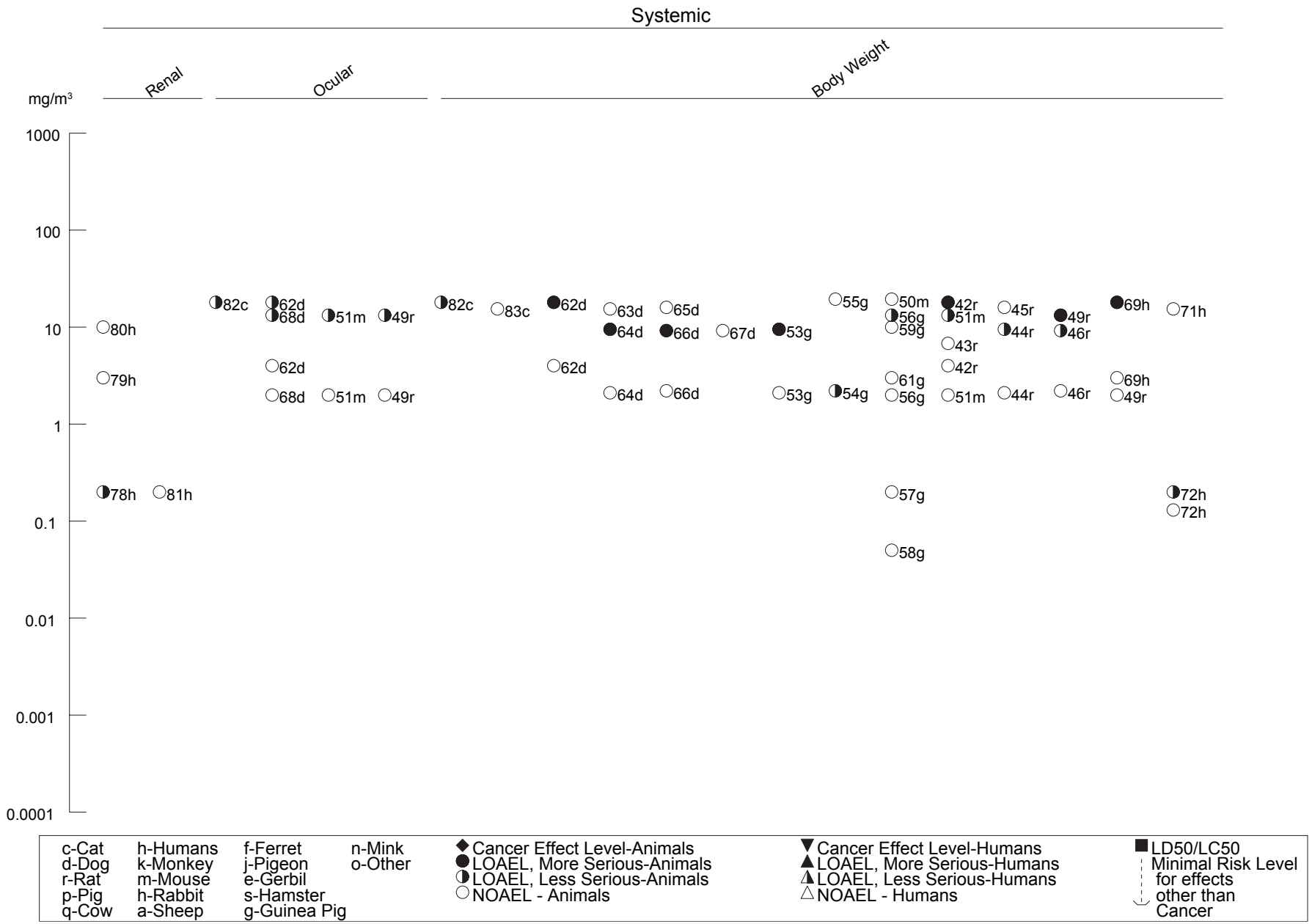
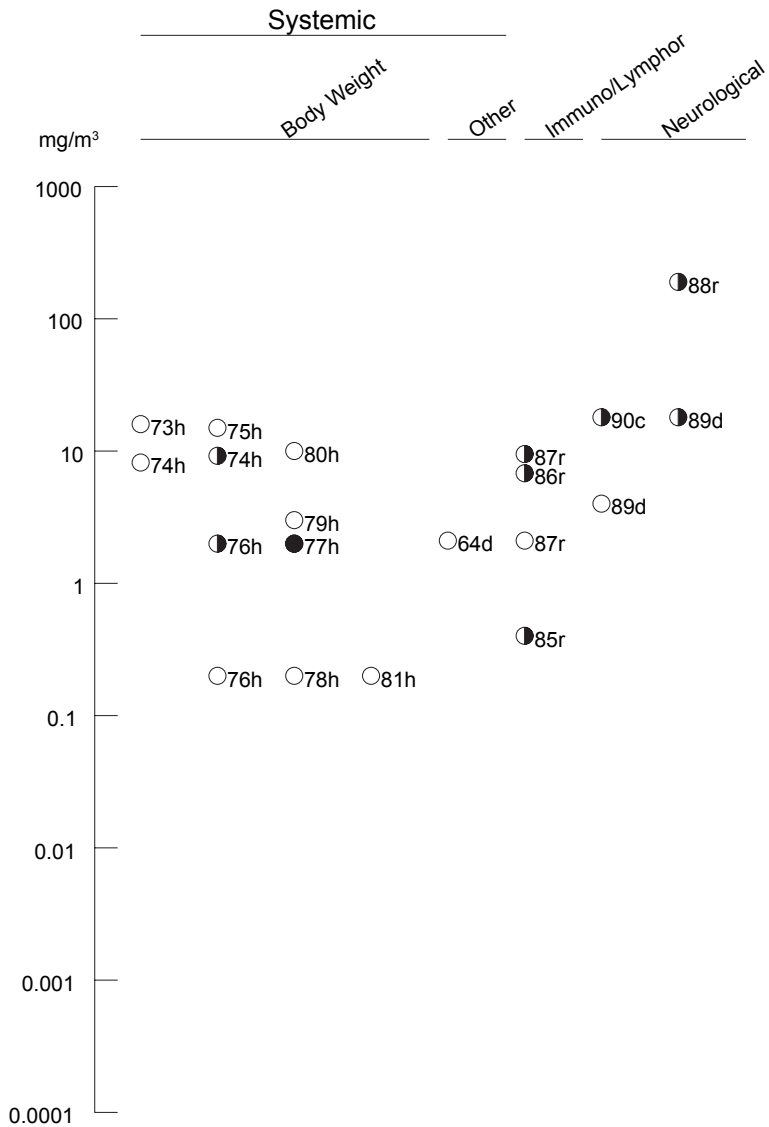


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Intermediate (15-364 days)



c-Cat h-Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◮ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Chronic (≥365 days)

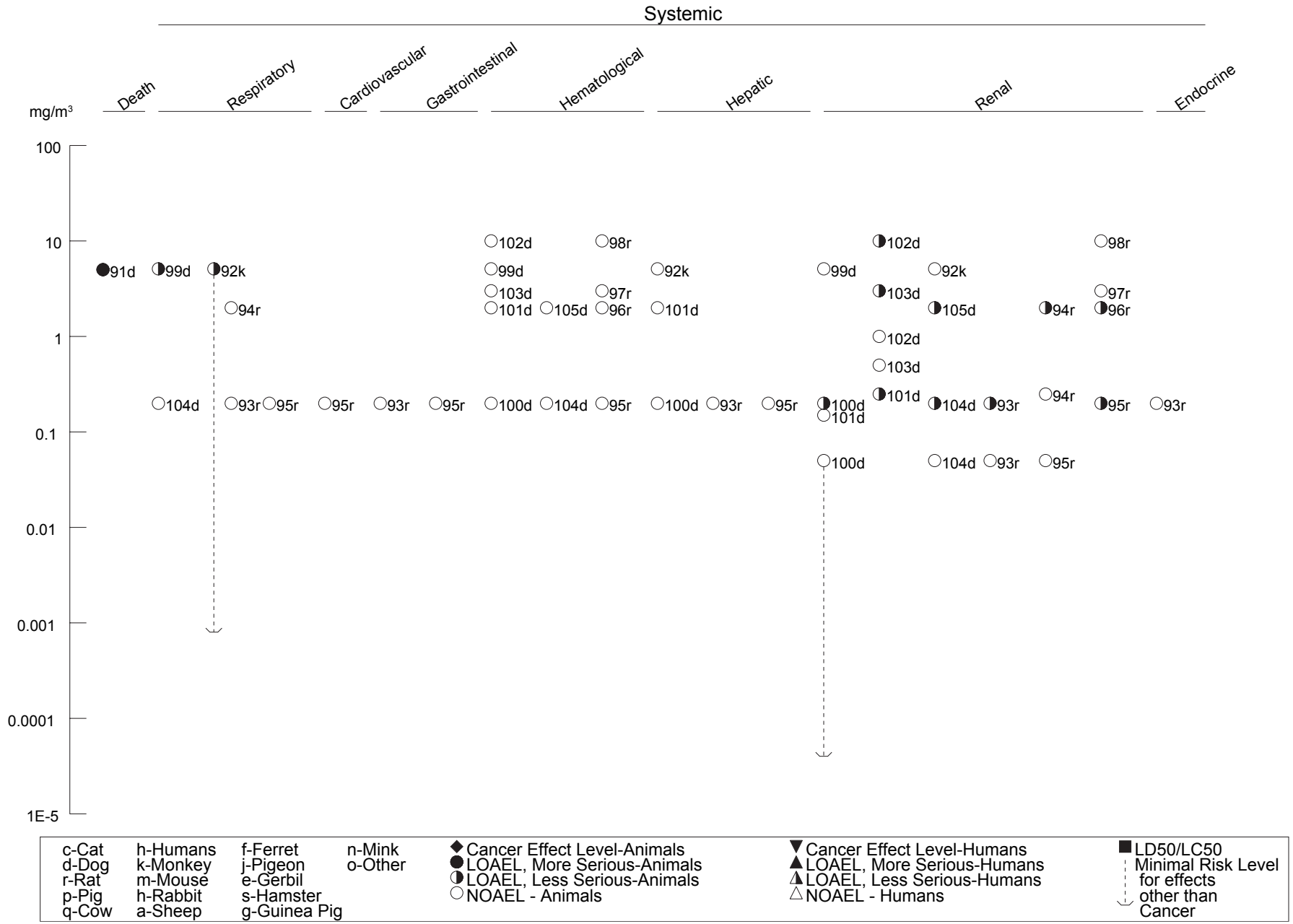
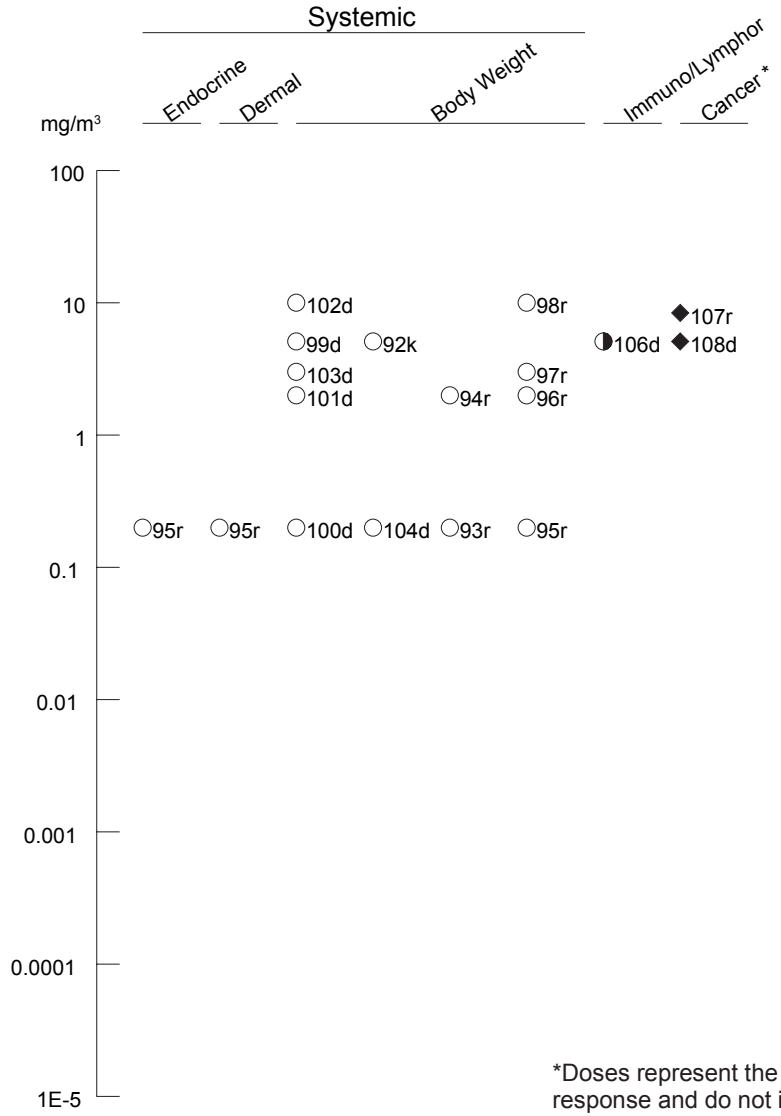


Figure 3-1 Levels of Significant Exposure to Uranium - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	h-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

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 3-1 and plotted in Figure 3-1.

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 size) are primarily 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 1994a; 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).

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.

In acute exposures, respiratory disease may be limited to interstitial inflammation of the alveolar epithelium, leading eventually to pulmonary fibrosis (Clayton and Clayton 1981; Cooper et al. 1982; Dungworth 1989; 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. 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 engine exhaust, cigarette smoke, and radon and its daughters), have been investigated. Several epidemiologic studies have reported respiratory diseases in uranium mine and mill workers, who were also exposed to significant amounts of dust and other pulmonary irritants, but not in uranium-processing workers, who were 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 (USNRC 1986, 1990). 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 1956). 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 (Cragle et al. 1988; NIOSH 1987; Polednak and Frome 1981; Scott et al. 1972).

A 30-year follow-up study (Dupree et al. 1987) 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 ratios [SMRs]=2.29) from obstructive pulmonary disease was found in 4,106 workers in a nuclear fuels fabrication plant who were employed for >6 months from 1956 to 1978 (Hadjimichael et al. 1983). However, the overall death rate and the rate of all cancers combined were lower than expected. The association of disease with exposure to uranium was not confirmed.

Pinkerton et al. (2004) reported significantly increased mortality from nonmalignant respiratory disease (100 observed vs. 70.16 expected; SMR 1.43, 95% CI 1.16–1.73) within a cohort of 1,485 workers employed in uranium mills in the Colorado Plateau region (Arizona, Colorado, New Mexico) when worker mortality was compared to mortality within the U.S. population. The workers were employed for at least 1 year; 37% were employed for 3–9 years and 20% for ≥10 years. The latency period (time from first employment to evaluation) was at least 20 years for 86% of the cohort. Mortality rates were not significantly elevated among the mill workers when compared to Colorado Plateau regional population mortality rates. This region is noted for relatively high chronic obstructive pulmonary disease compared to other states.

Boice et al. (2008) examined mortality in a cohort of mining (1,867 males and females) and milling (759 males and females) workers at Grants, New Mexico, compared to mortality rates for the U.S. population. All workers were employed for at least 6 months; 47 and 12% of the miners were employed for 0.5–1.9 and ≥10 years and 42 and 15% of the millers were employed for 0.5–1.9 and ≥10 years. For both groups, the latency period was ≥20 years. After separating the cohort according to type of employment (mining, milling), only the group that reported having worked in underground uranium mines exhibited significant excess mortality from nonmalignant respiratory disease (55 observed vs. 33.6 expected; SMR 1.64, 95% CI 1.23–2.13); the mortality ratio for the millers was 1.07 (25 observed vs. 23.4 expected; 95% CI 0.69–1.58). The increased mortality from nonmalignant respiratory disease among the workers with uranium mining experience is attributable to exposure to mining dusts, radon decay products, diesel exhaust, and excessive tobacco use, rather than exposure to uranium.

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 13.3 mg U/m^3 resulted in pulmonary edema, hemorrhage, emphysema, and inflammation of the bronchi and alveoli (Spiegl 1949). Exposure to 2.0 mg U/m^3 resulted in pulmonary edema, hemorrhage, and emphysema in rabbits and slight pneumonia in dogs (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 of exposure to 18 mg U/m^3 as uranium tetrafluoride (Dygert 1949a) and after 5 weeks of exposure to 9.2 mg U/m^3 as uranyl fluoride (Rothstein 1949a); the rhinitis was observed in animals dying early and were associated with other signs of morbidity. Histopathological evidence of toxicity was observed in several studies, including slight

degenerative changes in the lungs of 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. No histological damage attributable to uranium exposure were observed in the lungs. There was an absence of any other type of histological damage outside the kidneys (Cross et al. 1981a, 1981b; Stokinger et al. 1953). 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 4 hours/day, 5 days/week for 1–4 years 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 rats to 5.1 mg U/m^3 as uranium dioxide dust 5.4 hours/day, 5 days/week for 1 year did not result in histological damage in the lungs (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 (F344) male rats exposed, nose-only, for 100 minutes to an aerosol of to 92.8% ^{235}U-enriched uranium dioxide with a concentration ranging from 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 and the numbers of 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

[3]Type I cells are alveolar lining cells that are involved with the transfer of oxygen and other substances between the alveolus and the blood. Type II cells are alveolar cells involved in production and secretion of the surfactant coating the alveolar surface.

rats were further exposed to thermal 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 rad, 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).

However, another study (Morris et al. 1990) reported severe alveolar fibrosis or metaplasia in the lungs of three F344 rats nose-only exposed to an aerosol of 111–220 mg/m^3 92.8% enriched uranium dioxide for 100 minutes; AMAD of the particles ranged from 2.7 to 3.2 μm. The lung damage was observed only in animals sacrificed at 720 days postexposure; no effects were observed in animals examined ≤540 days postexposure. The α-particle radioactivity concentration was estimated as 1.91 kBq/g (51.6 nCi/mg) (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 rad (5 Gy) for the lungs and 7,000 rad (70 Gy) for the lymph nodes. Similarly exposed dogs also developed slight interstitial and vascular fibrosis of the lungs at lung following exposure to 5.1 mg U/m^3 with an estimated alpha-radiation tissue dose of 760–1,280 rad (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}Pu or ^{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 a review of the hazards associated with alpha-emitting radionuclide exposure, see 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 (Lu 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 (Lu 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 postaccident day 8, the clinical findings were loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool. On postaccident 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 International Commission on Radiological Protection (ICRP) lung model (ICRP 1994a) 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 1956; 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 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 from grooming of

uranium particulates deposited on the fur during the 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 (Stokinger et al. 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 who was accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Lu 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 insoluble uranium dust at 0.5–10 mg U/m^3 (Eisenbud and Quigley 1956).

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/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/day, 5 days/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/day 5 days/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/day

6 days/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 inhalation studies lasting 23–40 days, 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 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 (Rothermel 1949).

In chronic-duration exposures, dogs exposed to an airborne uranium 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 (Lu 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 exposed to 0.13 mg U/m^3 as uranyl nitrate 8 hours/day, 5 days/week for 30 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 (Rothermel 1949). Rabbits exposed to 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 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, it has been suggested that the renal damage from exposure to high-linear energy transfer coefficient (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 found no increased mortality in uranium workers due to renal disease (Archer et al. 1973a, 1973b; Checkoway et al. 1988; NIOSH 1987; Pinkerton et al. 2004; 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 comparison of kidney tissue obtained at autopsy from seven uranium workers and six 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 seven workers and four of six referents were categorized as abnormal. Uranium levels in the workers kidney tissue (estimated by alpha particle emission) ranged from 0.4 to 249 µg/kg. As reviewed by Eisenbud and Quigley (1956), no evidence of renal toxicity was observed in workers exposed to insoluble uranium compounds; 100 workers were exposed to 0.5–2.5 mg U/m^3 and another 50 workers were exposed to 2.5–10 mg U/m^3. Eisenbud and Quigley (1956) did not provide information on the parameters used to assess renal toxicity. A study on the kidney function of uranium mill workers chronically exposed to biologically soluble ammonium diuranate 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 mean (and median) urinary uranium levels were 65.2 µg/L (20 µg/L) in 1975 and 7.2 µg/L (6 µg/L) in 1981 after a new facility was built. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the area where yellowcake was dried and packaged in the old mill (prior to mid-1979) (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 postaccident day 68 as indicated by significantly elevated levels of urinary proteins, nonprotein nitrogen (NPN), and amino acid nitrogen/creatinine, and decreased phenol-sulfonpthalein excretion rate. These abnormalities persisted through day 1,065, but gradually returned to normal (Lu 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 postaccident day 1.

Renal effects were not observed in another accidental exposure (USNRC 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 to 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 kidney 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. 1982a; 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. 1982a). 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 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; Spiegl 1949; Stokinger et al. 1953). Soluble uranium compounds were more toxic, as evidenced by much lower LOAEL values, than the insoluble compounds. In an intermediate-duration inhalation exposure study, 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/day 6 days/week for approximately 30 days. The exposure resulted in severe degeneration and necrosis of the renal-cortical tubular epithelium, as well as 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 was noted 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/day, 5 days/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 one of the three 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 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, or 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 animals 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 mean NPN level in a control study performed in the same lab was approximately 32 mg% (Sprague 1949). 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 reduction 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 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 (Rothermel 1949) 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 NPN levels were normal (elevated blood NPN levels indicate a decrease in renal filtration capacity, similarly to elevated BUN). Observed changes in urinary protein were inconsistent and insignificant (Stokinger et al. 1953).

In another study, dogs of both sexes (9–12 males, 9–13 females) were exposed to concentrations of 0.04, 0.15, 0.25, or 2 mg U/m^3 as uranyl nitrate for 6 hours/day, 5.5 days/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 (Stokinger et al. 1953).

No treatment-related renal effects were seen in dogs 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). In similarly exposed Rhesus monkeys, blood NPN levels were consistently elevated; however, 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 exposed to 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 (Lu 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 uranium tetrachloride (Dygert 1949a). Ocular effects were due to direct contact of the eye with vapor or aerosols; because uranyl fluoride and hydrogen fluoride (a highly irritating chemical) are produced when uranium hexafluoride comes in contact with moisture, it is possible that uranium was not the causative agent for the ocular effects.

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 studies lasting 23–40 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/day, 5 days/week for 6 weeks) (Rothermel 1949; Rothstein 1949a, 1949b, 1949c; 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 of monkeys to concentrations of 3 mg U/m^3 as uranium dioxide 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/day, 5.5 days/week (Rothermel 1949).

3.2.1.3 Immunological and Lymphoreticular Effects

Although no studies were located that specifically tested immunological effects in humans following inhalation exposure to uranium, none of the epidemiologic studies of workers in uranium mines and fuel fabrication plants showed increased incidence of death due to diseases of the immune system (Checkoway et al. 1988; Keane and Polednak 1983; NIOSH 1987; 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 study investigators 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/day, 5 days/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/day, 5 days/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/day to 0.4 and 4 mg U/m^3 uranium tetrafluoride (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/day, 5 days/week for 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 five lobes of the lungs, was seen in F344 rats exposed to 6,825.5 nCi/m^3 through inhalation exposure to enriched uranium dioxide for 100 minutes (Morris et al. 1992). The radioactive material concentration of the mixture was estimated as 1.91 kBq/mg (51.6 nCi/mg); the degree of enrichment was calculated based on this specific activity. 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.

Albino HMT (F344) 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 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

A limited number of studies have examined the potential of uranium to induce neurological effects in humans or animals following inhalation exposure. In the available studies, 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 (Lu 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 (Carpenter et al. 1988; Cragle et al. 1988; NIOSH 1987; 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 of dogs exposed 8 hours/day, 5 days/week for 30 days to 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 18 mg U/m^3 as uranium tetrafluoride exhibited unsteady gait on the seventh day in a 30-day study (Dygert 1949a). In 5-week studies (8 hours/day, 5 days/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 neurological effects were observed in animals exposed to lethal concentrations.

In 12 rats exposed to 190 mg U/m^3 as depleted uranium dioxide 30 minutes/day, 4 days/week for 3 weeks, a significant increase in spontaneous activity (both locomotor and rearing behaviors) was observed on day 1 postexposure, but not on day 5 postexposure (Monleau et al. 2005). This appeared to correlate with a rapid reduction in uranium concentration in the hippocampus, frontal cortex, cerebellum, and olfactory bulb; with the exception of the hippocampus, brain uranium levels reached control levels by the 3rd postexposure day. A depression of spatial working memory was also observed on day 6 postexposure, but not on day 1 postexposure; no alterations in exploratory activity were observed.

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 3-1 and plotted in Figure 3-1.

3.2.1.5 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 that 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.

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 (Muller et al. 1967; Waxweiler et al. 1981b; Wiese and Skipper 1986). 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.

3.2.1.6 Developmental Effects

No studies were located that specifically reported effects of uranium on development in humans or animals following inhalation exposures for any duration. However, the issue of teratogenicity of depleted uranium aerosols in humans was reviewed by Hindin et al. (2005). The investigators examined a series of reports that included groups of Gulf War veterans from the United States, the United Kingdom, Canada, and Australia; reports from Iraqi hospitals and clinics during and after the war; reports of birth defects in a New Mexico community living near a depleted uranium weapons testing facility; reports of birth defects in infants born in Bosnia and Herzegovina after the Bosnia War or in Kuwait after the Gulf War; and other reports. Most of the data from these reports have not been published in peer-reviewed journals; some have been published in newspapers or presented at Iraqi conferences. Lacking from all reports was documentation of individual depleted uranium exposure and other wartime-generated substances, as well as nutritional and environmental factors. Some reports lacked methodologically rigorous investigation, while in others, the incidences of birth defects between purportedly exposed and nonexposed groups were not statistically significant. Of particular interest is a report from three major maternity hospitals in Basra, Iraq, which noted a dramatic increase in the incidence of total congenital malformations since the 1991 war. However, Hindin et al. (2005) note that very low incidence reported prewar often reached baseline Western levels by 1999–2000. Of note is the case of hydrocephalus, which the report of data through 2000 indicates no diagnosed cases of hydrocephalus between 1990 and 1998. This would mean that there were no cases of hydrocephalus among about 100,000 births, which was considered implausible. Hindin et al. (2005) raised the question of whether the detection of birth defects at the Basra study was less than complete, and if so, whether the omissions could have been systematic or random. In studies of Gulf War veterans, comparisons were made between deployed versus non-deployed, not necessarily between depleted uranium-exposed and non-depleted uranium-exposed; as such, the studies

are not very informative regarding the potential role of depleted uranium in inducing congenital malformations. Hindin et al. (2005) concluded that, overall, the epidemiological evidence is consistent with increased risk of birth defects in offspring from persons exposed to depleted uranium. However, given the limitations of the data described by the reviewers and confounders that were not addressed, the conclusion regarding birth defects may have overlooked other causes for the increase and overstated the data.

Similarly, Busby et al. (2010) examined the incidence of infant mortality and alterations in sex ratio in children living in Fallujah, Iraq using data collected from questionnaires completed by 711 households with 4,843 persons. An 18% reduction in male:female ratio from the expected ratio (1,055 boys to 1,000 girls) was found among children aged 0–4 years. In older children, the ratio was close to the expected level. An infant mortality (deaths between 0 and 1 year of age) ratio of 80 deaths per 1,000 was estimated. The authors state that this is significantly higher than infant mortality ratios in Egypt, Jordan, and Kuwait. However, the investigators did not evaluate the potential exposure for depleted uranium or have a comparable reference group (i.e., Iraqi households without the potential for exposure to depleted uranium), used a questionnaire to collect information on infant mortality and birth defects without confirmation from medical records, and collected data for a 10-year period but only used the last 5 years for the analysis; additionally, the investigators did not provide demographic data to support using infant mortality data from Egypt, Jordan, and Kuwait as an appropriate reference. The limitations of this study preclude using it to establish a causal relationship between exposure to depleted uranium and developmental toxicity.

3.2.1.7 Cancer

Human and animal studies have examined the potential carcinogenicity of uranium. 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). As discussed below, some studies have found significant increases in the risk of lung cancer, although it is not clear whether uranium is the causative agent and whether the cancer is due to chemical toxicity or radiotoxicity. In general, human and animal studies have not found increases in the risk of cancer in other tissues, including the kidney and bone.

Increased deaths from cancers of the respiratory tract (predominantly lung cancer) have been reported in numerous studies of uranium miners (Archer et al. 1973a; Auerbach et al. 1978; Band et al. 1982; Boice et al. 2008; Chovil and Chir 1981; Gottlieb and Husen 1982; Grace et al. 1980; Hornung and Meinhardt 1987; Hornung et al. 1998; Howe and Stager 1996; Howe et al. 1986, 1987; Kusiak et al. 1993; Lundin et al. 1969; Moolgavkar et al. 1993; Saccomanno et al. 1971, 1976, 1986, 1988, 1996; Samet et al. 1984a, 1984b, 1986, 1989, 1991, 1994; Ševc et al. 1993; Tirmarche et al. 1992, 1993; Tomášek et al. 2008; Waxweiler et al. 1981a; Whittemore and McMillan 1983; Woodward et al. 1991). However, the miners were exposed to cancer-inducing agents such as radon and its decay products, silica dust, arsenic, and diesel engine exhaust fumes. As discussed in the ATSDR Toxicological Profile for Radon (Agency for Toxic Substances and Disease Registry 2012), the increased lung cancer in uranium miners is attributable to exposure to radon and the additive effect of cigarette smoking, crystalline silica, and/or diesel engine exhaust rather than exposure to uranium. No alterations in deaths from bone or kidney cancer were observed in studies of uranium miners (Boice et al. 2008; Tirmarche et al. 1993; Waxweiler et al. 1981a).

Mortality has also been assessed in uranium mill workers without reported employment in uranium mining operations. A study of 662 male uranium mill workers employed at one of six uranium mills in the Colorado Plateau states (Colorado, Utah, New Mexico, Arizona) found a significant increase in death from tumors of the lymphatic and hematopoietic tissue (other than leukemia) during the period of 1950–1967 (4 observed vs. 1.02 expected; SMR 392; 95% CI not reported); the study authors noted that none of the four men worked near the fusion furnaces where exposure to concentrated uranium dust or fume was greatest (Archer et al. 1973b). Waxweiler et al. (1983) performed a study that included 2,002 uranium millers employed at one of seven uranium mills in the Colorado Plateau states for at least 1 year after January 1, 1940; a nonsignificant excess of deaths from lymphatic malignancies other than leukemia (7 deaths vs. 5.6 expected) was reported for the period through 1977. When divided by latency period, excess risk (6 deaths vs. 2.6 expected) was only found at >20 years. No significant alterations in lung cancer risk was found. Pinkerton et al. (2004) reevaluated the cohort described by Waxweiler et al. (1983) and determined that a total of 1,484 men fit the criteria for inclusion; most of the workers were employed for <9 years, 42.7% were employed for 1–2 years. Nonsignificant excesses of mortality from lymphatic and hematopoietic malignancies other than leukemia (16 observed vs. 11.08 expected; SMR 1.44; 95% CI 0.83–2.35) and from respiratory cancers that included trachea, bronchus, and lung (78 observed vs. 68.93 expected; SMR 1.13; 95% CI 0.89–1.41) and a significant decrease in digestive systems cancers (33 observed vs. 53.18 expected; SMR 0.62; 95% CI 0.43–0.87) were reported through 1998. Mortality from these diseases did not increase with length of employment, and mortality from lung cancer was higher among workers hired prior to 1955 when exposures to uranium, silica, and vanadium

were presumably higher. Interpretation of the results of these studies of uranium mill workers is limited due to relatively small cohort sizes, inability to estimate individual exposures, and lack of smoking data.

Boice et al. (2008) conducted a cohort mortality study of workers engaged in uranium mining and milling activities near Grants, New Mexico between 1955 and 1990. Vital status was determined through 2004 and SMRs were calculated for 2,745 workers (2,500 males, 245 females) alive after 1978 who were employed for at least 6 months. No significant increases in cancer mortality were observed in 904 uranium milling workers who were not known to have worked at a mine or 106 workers whose mining experience was not known. Based on national mortality rates, mortality from respiratory cancers (bronchus, trachea, lung) was significantly higher than expected among the uranium mining and milling workers known to have been employed in an underground uranium mine (n=1,735) (SMR 2.17; 95% CI 1.75–2.65). Therefore, the observed increased cancer mortality was considered attributable to historically high levels of radon in the mines combined with heavy use of tobacco products and co-exposure to crystalline silica and diesel exhaust. Deaths from other types of cancer were not significantly increased in the whole cohort or either subcohort.

Cancer mortality has been assessed in studies of populations living near uranium mining and milling facilities in Uravan, Colorado (Boice et al. 2007a), Montrose County, Colorado (Boice et al. 2007b), Karnes County, Texas (Boice et al. 2008), Grants, New Mexico (Boice et al. 2010), and Monticello, Utah (UDOH 2007). Compared to U.S. mortality rates, no significant increase in mortality from cancers was observed among the residents of Uravan, Colorado, or among 622 of the residents who had been employed in uranium mills. A significant increase in lung cancer (SMR 2.00; 95% CI 1.39–2.78) was found among 459 residents who had worked in underground uranium mines and was attributed to historically high levels of radon in the mines coupled with heavy use of tobacco products. Similarly, increased mortality from lung cancer was noted in males living in Montrose County, Colorado, and Grants, New Mexico, but not in females. Occupational exposure to radon and smoking among underground uranium mine workers was considered to be the cause of the increased mortality from lung cancer within the population of male residents. The female population of Grants, New Mexico exhibited a significant excess of mortality from stomach cancer (SMR 1.30; 95% CI 1.03–1.63), which declined over the 55-year observation period; the stomach cancer increase was highest before the uranium mining and milling operations began and then decreased to normal levels, indicating that these operations were not the source of the increased mortality from stomach cancer. No unusual patterns of cancer mortality were observed in residents of Karnes County, Texas from 1950 to 2001 (Boice et al. 2003). Among residents of Monticello, Utah, a significant increase in the incidence of lung and bronchial cancer was

found for three analytical periods (1973–2004, 1998–2004, and 1993–1997); the standardized incidence ratio (SIR) for the 1973–2004 period was 1.94 (95% CI 1.24–2.79) (UDOH 2007). An increase in stomach cancer risk (SIR 6.14; 95% CI 1.60–13.63) was also found for the 1998–2004 evaluation period; however, the small number of observed cases reduces the reliability of the significant SIR. Interpretation of the results of this study is limited by the small number of subjects and the lack of control for potential risk factors such as smoking and family history. In addition to potential uranium exposure, past monitoring data of on- and off-site soil samples and off-site air samples have found elevated levels of radium, radon, beryllium, chromium, lead, nickel, and thallium.

The issue of cancer risk in nuclear workers occupationally exposed to uranium has recently been reviewed by Canu et al. (2008). The authors reviewed 23 epidemiological studies: 18 cohort studies and 5 nested case-control studies published since 1980. The overall conclusion was that the epidemiological studies provide limited evidence of a relationship between site-specific cancer mortality and internal exposure to uranium and mixed fission products. The authors identified three main limitations common to almost all studies: limited statistical power, relatively low radiation doses, and inaccurate exposure assessment. A more recent study of gaseous diffusion workers (Chan et al. 2010) did not find a significant increase in deaths from all cancers or a specific type of cancer when all workers were combined. The investigators used a surrogate measure (μg/year) estimated from urine data to represent cumulative dose of internally deposited radionuclides; however, since this is not a unit of measure for radiation, it is unclear what was actually measured. The workers were exposed to arsenic, beryllium, chromium, nickel, and uranium. A significant increase in the risk of non-Hodgkin's lymphoma were observed in workers with cumulative internal radiation exposures of 21–50 or 51–125 μg/year, but not in workers with the highest cumulative exposure (>125 μg/year). No significant increases in the risk of non-Hodgkin's lymphoma were found when the workers were divided by cumulative external radiation quartiles. When workers were divided by the levels of individual metal exposures, a near significant increase in lung cancer (standardized rate ratio [SRR] 1.17; 95% CI 0.99–1.38) was noted in workers with medium exposure to uranium. An increase in lung cancer risk was also observed in workers with medium exposure to nickel. Interpretation of the results of this study is limited by the lack of exposure information and due to co-exposure to other metals including arsenic, beryllium, chromium, and nickel and co-exposure to radiation. Another study of gaseous diffusion workers (Yiin et al. 2009), found a marginally increased risk of multiple myeloma among the workers (odds ratio of 1.04; 95% CIs 1.00–1.09; with adjustment for age, combined x-ray and external radiation exposures, and chemical exposures) at a radiation dose of 10 μGy to bone marrow estimated from uranium urinalysis measurements.

Busby et al. (2010) examined the relative risk of cancer among residents living in Fallujah, Iraq between 2005 and 2010; data were collected from questionnaire completed by 711 households with 4,843 persons. As compared to cancer rates from Egypt in 1999, significant increases in the risk of several cancers, including childhood cancers, breast cancer, leukemia, lymphoma, and brain cancer, were observed. As with the developmental toxicity portion of this study, the investigators did not provide uranium exposure level or support for the assumption that the residents were exposed to uranium. Additionally, the study did not involve a comparison between cancer incidences in Fallujah with other Iraqi populations not exposed to uranium and cancer incidences were based on self-reported data without confirmation from medical records. These limitations preclude establishing a causal relationship between increased cancer risk and uranium exposure.

A study of groups of 102 male 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 show signs of cancer development upon examination of selected tissues including lungs, trachea, liver, kidneys, spleen, heart, and any abnormal tissue (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 >8,000 WLMs. 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. No significant alterations in the incidence on nonpulmonary neoplasms were observed in any exposure group, as compared to the unexposed controls.

Pulmonary adenomas or adenocarcinomas were observed in 4/13 Beagle dogs exposed to 5.1 mg U/m^3 as uranium dioxide for 5 years (Leach et al. 1973). The neoplasms were observed 22–67 months after exposure termination. The lung dose was estimated as 600–700 rad (6–7 Gy). Spontaneous tumors are rarely found in dogs, and the incidence found in this study was 50–100 times higher than the expected rate of spontaneous tumors. No pulmonary neoplasms were observed in six monkeys similarly exposed to 5.1 mg U/m^3 as uranium dioxide for 5 years (Leach et al. 1973).

A study was conducted with uranium ore dust in male Sprague-Dawley rats (Mitchel et al. 1999). The rats were exposed nose-only to uranium ore dust that was delivered to the rats as an aerosol under positive pressure. The ore was without significant radon content. The rats were exposed to 0, 8.4, or 22 mg U/m^3 4.2 hours/day, 5 days/week for 65 weeks and were allowed to live for their natural lifetime. Exposure to uranium significantly increased the incidence of malignant and nonmalignant lung tumors. The frequency of primary malignant lung tumors was 0.016, 0.175, and 0.328 and the frequency of nonmalignant lung tumors was 0.016, 0.135, and 0.131 in the control, low- and high-dose groups, respectively. The main malignant tumor was bronchioalveolar carcinoma. No bronchial lymph node tumors were detected even though the lymph node specific burdens were considerably higher than in the lung in the same animal. The average absorbed doses for the low- and high-dose groups were 0.87 and 1.64 Gy, respectively, resulting in an average risk of malignant lung tumors of about 0.20 tumors per animal per Gy in both exposed groups. Lung tumor frequency was not directly proportional to dose, but exhibited a direct linear relationship with dose rate (as measured by the lung burden at the end of dust inhalation). Mitchel et al. (1999) noted that this suggested that lung burden may be the more important determinant of lung cancer risk.

Cancer Effect Levels (CELs) for chemical and radiation inhalation exposure to uranium are shown in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

The oral toxicity of uranium compounds has been evaluated in several animal species following exposure in drinking water or via gavage. The oral exposure studies did not report baseline uranium levels in the diet or drinking water; thus, baseline exposures were not included in the estimated doses. The levels of uranium in the drinking water may vary according to the source of the water (e.g., tap water, mineral water) and some sources may have naturally high levels of uranium; if provided, the source of the drinking water was included in the discussion of individual studies. 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 three soluble compounds (uranyl nitrate hexahydrate, uranyl tetrafluoride, and uranium tetrachloride) and 20% uranium compound for the three 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); and practically nontoxic compounds were uranium tetrafluoride, triuranium octaoxide, and uranium dioxide (Maynard and Hodge 1949).

3.2.2.1 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, and 28 mg U/kg/day uranium as uranyl acetate dihydrate by gavage in water from gestation day 13 through postnatal day 21. Two dams in the 2.8 mg U/kg/day group and three in the 28 mg U/kg/day group 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 et al. 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 3-2 and plotted in Figure 3-2.

3.2.2.2 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.

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 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to Uranium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				114 M (LD50)	Domingo et al. 1987 Uranyl Acetate	
2	Rat (NS)	once (F)				664 (16% mortality)	Maynard et al. 1953 Uranyl Nitrate	
3	Mouse (Swiss-Webster)	once (GW)				136 M (LD50)	Domingo et al. 1987 Uranyl Acetate	
4	Mouse (BALB/c)	once (G)				166 M (100% mortality 3 days post exposure)	Martinez et al. 2003 Uranyl Nitrate	
Systemic								
5	Human	once (W)	Gastro		14.3 M (nausea, vomiting, diarrhea)		Butterworth 1955 Uranyl Nitrate	
6	Rat (Long- Evans)	2 wk ad lib (W)	Bd Wt	14 M		28 M (53% reduced body weight gain)	Briner and Murray 2005 Depleted uranyl acetate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Sprague-Dawley)	once (GW)	Hepatic		118 M (microhemorrhagic foci)		Domingo et al. 1987 Uranyl Acetate	
			Renal		118 M (Increased urine volume, increased plasma creatinine and urea, increased urinary total protein and creatinine, and minimal histological lesions)			
			Bd Wt			118 M (weight loss)		
8	Rat (Sprague-Dawley)	1 or 3 d (GW)	Metab		97 M (alterations in serum 1,25(OH)2 vitamin D levels)		Tissandie et al. 2006 Uranyl Nitrate	
9	Mouse (BALB/c)	once (G)	Renal			166 M (increased blood urea and creatinine levels, tubular necrosis)	Martinez et al. 2003 Uranyl Nitrate	
10	Mouse (Swiss)	5 d (F)	Renal		508 M (increased blood urea nitrogen, creatinine, and alkaline phosphatase levels)		Ozmen and Yurekli 1998 Uranyl Nitrate	
			Bd Wt	508 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
11	Rat (Long- Evans)	2 wk ad lib (W)		14 M	28 M (increased open field activity)		Briner and Murray 2005 Depleted uranyl acetate	
12	Mouse (Swiss-Webster)	2 wk ad lib (W)			6 F (increased open field activity)		Briner 2009 Depleted uranyl acetate	
Developmental								
13	Rat (Wistar)	once (GW)			42.7 (delayed tooth eruption and development in neonatal rats)		Pujadas-Bigi et al. 2003 Uranyl Nitrate	
14	Mouse (Swiss-Webster)	Gd 6-15 (GW)			2.8[b] (decreased fetal BW; increased incidence of external defects)		Domingo et al. 1989c Uranyl Acetate	
INTERMEDIATE EXPOSURE								
Death								
15	Rat (NS)	30 d (F)				827 M (LD50)	Maynard and Hodge 1949 Uranium Peroxide	
16	Rat (NS)	30 d (F)				658 M (LD50) 1096 F (LD50)	Maynard and Hodge 1949 Uranium Tetrachloride	
17	Rat (NS)	30 d (F)				541 (LD50)	Maynard and Hodge 1949 Uranyl Fluoride	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (NS)	30 d (F)				7858 M (100% mortality) 1103 F (LD50)	Maynard and Hodge 1949 Uranyl Acetate	
19	Rat (NS)	30 d (F)				1579 (LD50)	Maynard and Hodge 1949 Uranyl Nitrate	
20	Rat (NS)	30 d (F)				664 (increased mortality)	Maynard et al. 1953 Uranyl Nitrate	
21	Mouse (Swiss-Webster)	30 d 1x/d (G)				2.8 F (10% mortality)	Domingo et al. 1989b Uranyl Acetate	
22	Mouse (dba)	48 wk ad lib (F)				452 F (8% mortality)	Tannenbaum et al. 1951 Uranyl Fluoride	
23	Mouse (dba)	48 wk ad lib (F)				925 F (24% mortality)	Tannenbaum et al. 1951 Uranyl Nitrate	
24	Dog (Beagle)	30 d 6 d/wk (F)				440 (lethal dose)	Maynard and Hodge 1949 Uranium Dioxide	
25	Dog (Beagle)	30 d 6 d/wk (F)				390 (lethal dose)	Maynard and Hodge 1949 Uranium Peroxide	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
26	Dog (Beagle)	30 d 6 d/wk (F)				5653	(lethal dose)	Maynard and Hodge 1949 Triuranium Octoxide	
27	Dog (Beagle)	30 d 6 d/wk (F)				63	(lethal dose)	Maynard and Hodge 1949 Uranium Tetrachloride	
28	Dog (Beagle)	30 d 6 d/wk (F)				15.4	(lethal dose)	Maynard and Hodge 1949 Uranyl Fluoride	
29	Dog (Beagle)	30 d 6 d/wk (F)				237	(lethal dose)	Maynard and Hodge 1949 Uranyl Nitrate	
30	Dog (NS)	138 d (F)				95	(lethal dose)	Maynard and Hodge 1949 Uranyl Nitrate	
31	Dog (Beagle)	30 d 6 d/wk (F)				191	(lethal dose)	Maynard and Hodge 1949 Ammonium Diuranate	
32	Dog (Beagle)	30 d 6 d/wk (F)				190	(lethal dose)	Maynard and Hodge 1949 Sodium Uranate	
33	Rabbit (NS)	30 d (F)				14.2	(67% mortality)	Maynard and Hodge 1949 Uranyl Nitrate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
34	Rat (Sprague-Dawley)	1.5 mo ad lib (W)	Bd Wt	2 M			Bensoussan et al. 2009 Uranyl Nitrate	
35	Rat (Sprague-Dawley)	9 mo (W)	Hemato		2.4 M (20% decreased in erythrocyte levels)		Berradi et al. 2008 Depleted uranyl nitrate	
			Renal		2.4 M (tubulointerstitial lesions)			
36	Rat (Long- Evans)	6 mo ad lib (W)	Bd Wt	14 M		28 M (46% reduced body weight gain)	Briner and Murray 2005 Depleted uranyl acetate	
37	Rat (Sprague-Dawley)	9 mo ad lib (W)	Bd Wt		2.7 M (11% reduced final body weight)		Bussy et al. 2006 Depleted uranyl nitrate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Rat (Sprague-Dawley)	28 d (W)	Resp	35.3 M			Gilman et al. 1998a Uranyl Nitrate	
			Cardio	35.3 M				
			Gastro	35.3 M				
			Hemato	35.3 M				
			Musc/skel	35.3 M				
			Hepatic	35.3 M				
			Renal	35.3 M	40 F (39% increase in serum uric acid)			
			Endocr	35.3 M				
			Bd Wt	35.3 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Rat (Sprague-Dawley)	91 d (W)	Resp	36.73 M			Gilman et al. 1998a Uranyl Nitrate	
			Cardio	36.73 M				
			Gastro	36.73 M				
			Hemato	36.73 M				
			Musc/skel	36.73 M				
			Hepatic		0.06 M (anisokaryosis, vesiculation, increased portal density, perivenous vacuolation and homogeneity)			
			Renal		0.06 M[c] (nuclear vesiculation, cytoplasmic vacuolation, tubular dilation, interstitial lymphoid cuffing)			
			Endocr	0.06 M 0.42 F	0.31 M (multifocal reduction of follicular size, increased epithelial height in thyroid, decreased amount and density of colloid)			
					2.01 F (multifocal reduction of follicular size, increased epithelial height in thyroid, decreased amount)			
			Bd Wt	36.73 M				
			Other	7.54 M	36.73 M (sinus hyperplasia in spleen)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Rat (Sprague-Dawley)	3 months ad lib (W)	Bd Wt	22.5 M			Linares et al. 2005 Uranyl Acetate	
41	Rat (NS)	30 d (F)	Bd Wt			6637 (retarded growth)	Maynard et al. 1953 Uranyl Nitrate	
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 Uranyl Acetate	
			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	Rat (Sprague-Dawley)	9 mo (W)	Hepatic	1 M			Racine et al. 2010 Depleted uranyl nitrate	
			Metab		1 M (altered cholesterol catabolism)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
44	Rat (Sprague-Dawley)	90 months (W)	Renal	2.3 M			Rouas et al. 2011 Depleted uranyl nitrate	
45	Rat (Sprague-Dawley)	9 mo (W)	Metab		2.4 M (decreased 1,25(OH)vitamin D3 levels)		Tissandie et al. 2007 Depleted uranyl nitrate	
46	Mouse (C57BL/6N)	15 wk ad lib (W)	Bd Wt	100 F			Arnault et al. 2008 Uranyl Nitrate	
47	Mouse (B6C3F1)	30 d ad lib (W)	Bd Wt	9.3 F			Raymond-Whish et al. 2007 Depleted uranyl nitrate	
48	Mouse (dba)	48 wk ad lib (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum et al. 1951 Uranyl Fluoride	
49	Mouse (C3H)	18 wk ad lib (F)	Bd Wt	925 F			Tannenbaum et al. 1951 Uranyl Nitrate	
			Other	925 F				
50	Mouse (C3H)	48 wk ad lib (F)	Renal		452 M (nodular development on kidney surface)		Tannenbaum et al. 1951 Uranyl Fluoride	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Mouse (dba)	48 wk ad lib (F)	Bd Wt	462 F			Tannenbaum et al. 1951 Uranyl Nitrate	
			Other	462 F				
52	Rabbit (New Zealand)	91 d (W)	Resp	28.7 M			Gilman et al. 1998b Uranyl Nitrate	
			Cardio	28.7 M				
			Gastro	28.7 M				
			Hemato	28.7 M				
			Musc/skel	28.7 M				
			Hepatic	28.7 M				
			Renal		0.05 M (cytoplasmic vacuolization, anisokaryosis, nuclear vesiculation)			
					0.49 F (anisokaryosis, nuclear vesiculation, atrophy)			
			Endocr	28.7 M				
			Bd Wt	28.7 M				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
53	Rabbit (New Zealand)	91 d (W)	Resp	40.98 M			Gilman et al. 1998c Uranyl Nitrate	
			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 (	40.38 M (glycosuria, proteinuria, anisokaryosis, nuclear hyperchromicity, nuclear pyknosis, tubular atrophy)			
			Endocr	40.98 M				
			Bd Wt	40.98 M				
			Other	40.98 M				
Neurological								
54	Rat (Sprague-Dawley)	3 mo ad lib (W)		22.4 M			Belles et al. 2005 Uranyl Acetate	NOAEL is for behavioral effects.
55	Rat (Sprague-Dawley)	1.5 mo ad lib (W)			2 M (cholinergic alterations in the brain)		Bensoussan et al. 2009 Uranyl Nitrate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
56	Rat (Long- Evans)	6 mo ad lib (W)		14 M	28 M (increased motor activity)		Briner and Murray 2005 Depleted uranyl acetate	
57	Rat (Sprague-Dawley)	9 mo ad lib (W)			2.7 M (altered neurotransmitter levels in the brain)		Bussy et al. 2006 Depleted uranyl nitrate	
58	Rat (Sprague-Dawley)	1.5 mo ad lib (W)			2.7 (sleep and behavioral alterations)		Houpert et al. 2005 Enriched Uranyl Nitrate	
59	Rat (Sprague-Dawley)	1.5 mo ad lib (W)		2.7			Houpert et al. 2005 Depleted uranyl nitrate	
60	Rat (Sprague-Dawley)	9 mo ad lib (W)			2.5 M (decreased spatial working memory)		Houpert et al. 2007b Enriched Uranyl Nitrate	
61	Rat (Sprague-Dawley)	90 days (W)			3.7 M (increase in REM sleep)		Lestaevel et al. 2005a Depleted uranyl nitrate	
62	Rat (Sprague-Dawley)	90 d ad lib (W)			5.6 M (increased oxidative stress in brain areas).		Linares et al. 2007 Uranyl Acetate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
63	Rat (Sprague-Dawley)	28 d (W)		35.3 M 40 F			Gilman et al. 1998a Uranyl Nitrate	
64	Rat (Sprague-Dawley)	91 d (W)		36.73 M 53.56 F			Gilman et al. 1998a Uranyl Nitrate	
65	Rat (Sprague-Dawley)	9 mo ad lib (W)		1.9 M			Grignard et al. 2008 Depleted uranyl nitrate	NOAEL is for blood levels of testosterone and 17B-estradiol.
66	Rat (Sprague-Dawley)	9 mo ad lib (W)			1.9 M (3-fold increase in plasma testosterone)		Grignard et al. 2008 Enriched Uranyl Nitrate	
67	Rat (Sprague-Dawley)	3 months ad lib (W)		5.6 M	11.2 M (reduced pregnancy rate)		Linares et al. 2005 Uranyl Acetate	
68	Mouse (C57BL/6N)	15 wk ad lib (W)			1.25 F (slight disturbance in ovarian folliculogenesis)		Arnault et al. 2008 Uranyl Nitrate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
69	Mouse (Hybrid)	49 d ad lib (W)		1.9 F	3.9 F (increased proportion of morphologically abnormal oocytes)		Feugier et al. 2008 Uranyl Nitrate	
70	Mouse (Swiss-Webster)	40 d ad lib (W)			2.5 F (increased oocyte dysmorphism and micronuclei in cumulus cells)		Kundt et al. 2009 Uranyl Nitrate	
71	Mouse (Swiss-Webster)	64 d (W)			5.6 M (significantly reduced pregnancy rate)		Llobet et al. 1991 Uranyl Acetate	
72	Mouse (Swiss-Webster)	60 d (G)		14			Paternain et al. 1989 Uranyl Acetate	NOAEL is for fertility.
73	Rabbit (New Zealand)	91 d (W)		28.7 M 43.02 F			Gilman et al. 1998b Uranyl Nitrate	
Developmental								
74	Rat (Sprague-Dawley)	132 d (W)			4.3 F (delayed hyperactivity; decreased spatial working memory)		Houpert et al. 2007a Enriched Uranyl Nitrate	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
75	Rat (Sprague-Dawley)	70 d ad lib (W)			22.5 (13-16% reduction in pups weight on day 21)		Sanchez et al. 2006 Uranyl Acetate	
76	Mouse (C57BL/6N)	15 wk ad lib (W)			1.25 F (slight disturbance in ovarian folliculogenesis)		Arnault et al. 2008 Uranyl Nitrate	
77	Mouse (Swiss-Webster)	30 d 1x/d (G)				28 (decrease in litter size on PND 21; decreased day 21 viability index)	Domingo et al. 1989b Uranyl Acetate	
78	Mouse (Swiss-Webster)	27 d (G)		5.6 F		14 F (increased late resorptions and decreased live fetuses)	Paternain et al. 1989 Uranyl Acetate	
79	Mouse (Swiss-Webster)	56 d (G)			2.8 F (reduced pup's weight on PND 21)	5.6 F (increased neonatal death per litter)	Paternain et al. 1989 Uranyl Acetate	
CHRONIC EXPOSURE								
Death								
80	Rat (NS)	2 yr (F)				270 (50% mortality within first year)	Maynard and Hodge 1949; Maynard et al. 1953 Uranyl Fluoride	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
81	Rat (NS)	2 yr (F)				660 M (70% mortality after 20 months)	Maynard and Hodge 1949; Maynard et al. 1953 Uranyl Nitrate	
Systemic								
82	Rat (NS)	2 yr (F)	Resp	660			Maynard and Hodge 1949; Maynard et al. 1953 Uranyl Nitrate	
			Cardio	660				
			Gastro	660				
			Hemato	170 F	330 F (slight decr RBCs and hemoglobin)			
			Hepatic	660				
			Renal	33	170 (minimal renal tubular damage)			
			Endocr	660				
			Bd Wt	170 M	330 M (11% decr BW gain)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
83	Rat (NS)	2 yr (F)	Resp	270			Maynard and Hodge 1949; Maynard et al. 1953 Uranyl Fluoride	
			Cardio	270				
			Gastro	270				
			Hemato	81 M	140 M (decr RBC and hemoglobin; incr WBC)			
			Hepatic	270				
			Renal	54	81 (minimal tubular alterations)			
			Endocr	270				
			Bd Wt	81	140 (11-15% decr BW gain)	270 (28-30% decrease in BW gain)		

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
84	Rat (NS)	2 yr (F)	Resp	12000			Maynard and Hodge 1949; Maynard et al. 1953 Uranium Dioxide	
			Cardio	12000				
			Gastro	12000				
			Hemato	12000				
			Hepatic	12000				
			Renal	12000				
			Endocr	12000				
			Bd Wt	12000				
85	Rat (NS)	2 yr (F)	Resp	11000			Maynard and Hodge 1949; Maynard et al. 1953 Uranium Tetrafluoride	
			Cardio	11000				
			Gastro	11000				
			Hemato	11000				
			Hepatic	11000				
			Renal	1100	11000	(mild renal tubular degeneration)		
			Endocr	11000				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
			Bd Wt	1100	11000	(10% decr BW gain after 1 year)		

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

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.002 mg/kg/day for soluble uranium compounds based on a BMDL0.05 of 0.20 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

c Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.0002 mg/kg/day for soluble uranium compounds based on a LOAEL of 0.06 mg/kg/day and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PND = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

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

Acute (≤14 days)

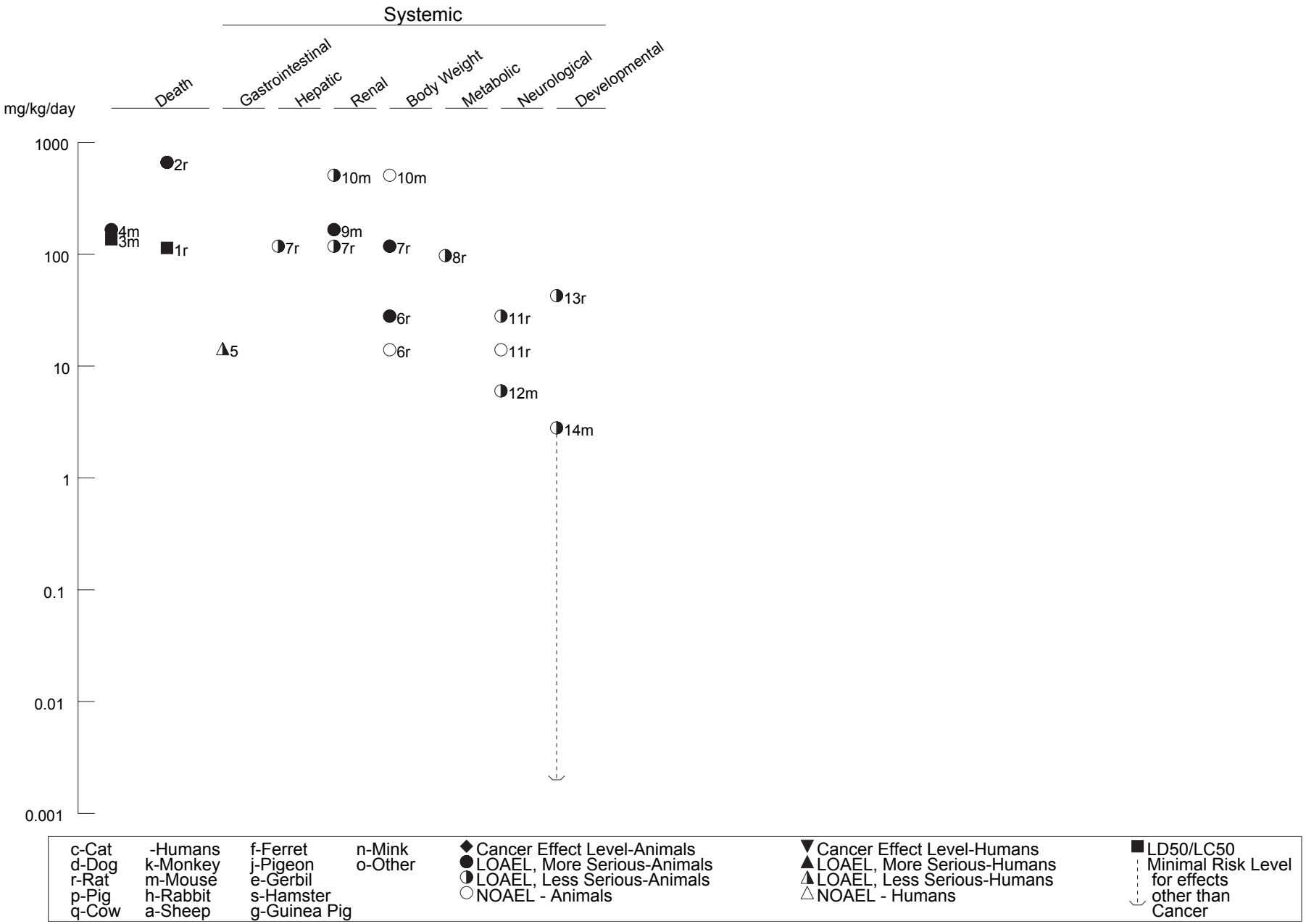


Figure 3-2 Levels of Significant Exposure to Uranium - Oral *(Continued)*

Intermediate (15-364 days)

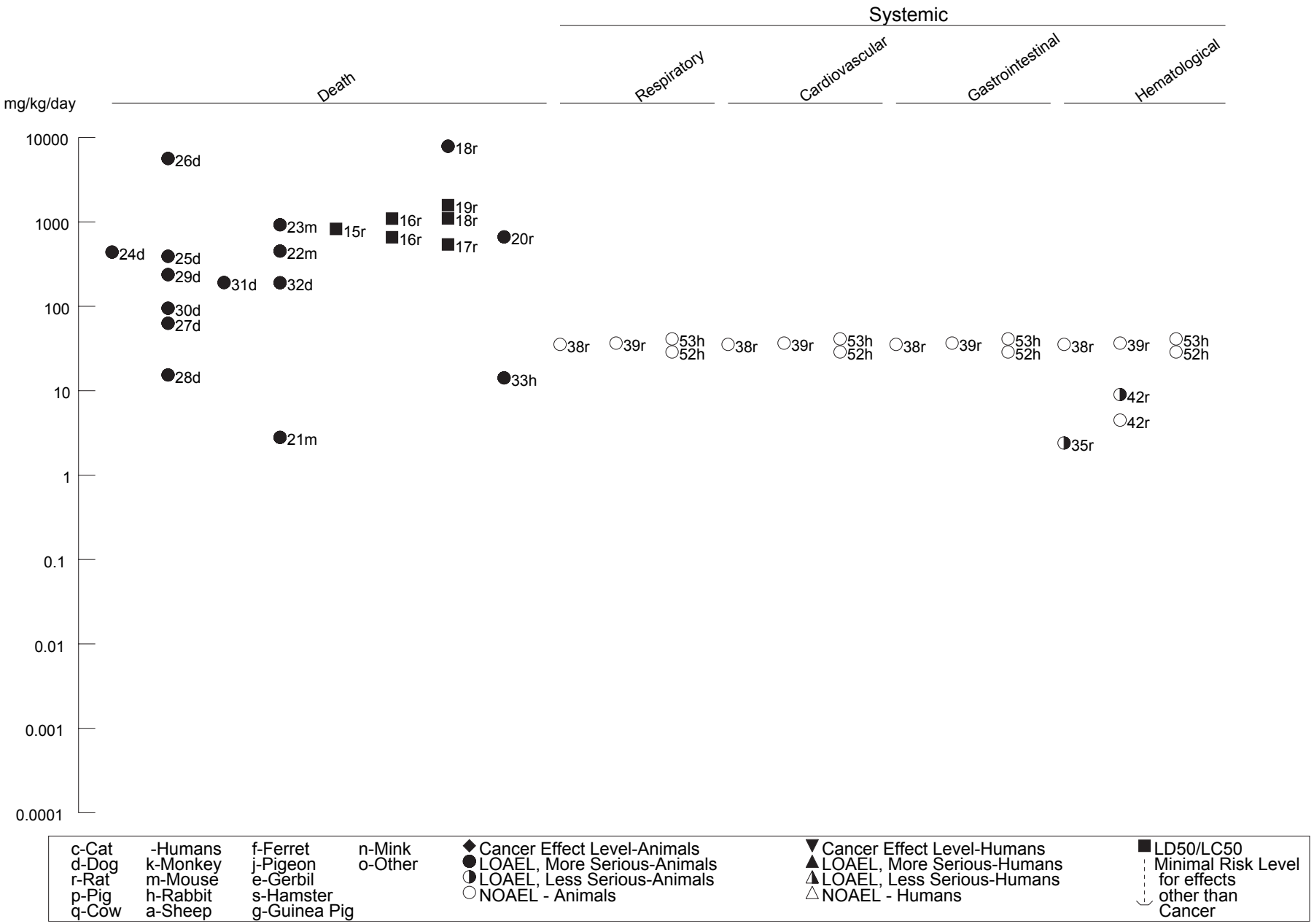


Figure 3-2 Levels of Significant Exposure to Uranium - Oral *(Continued)*

Intermediate (15-364 days)

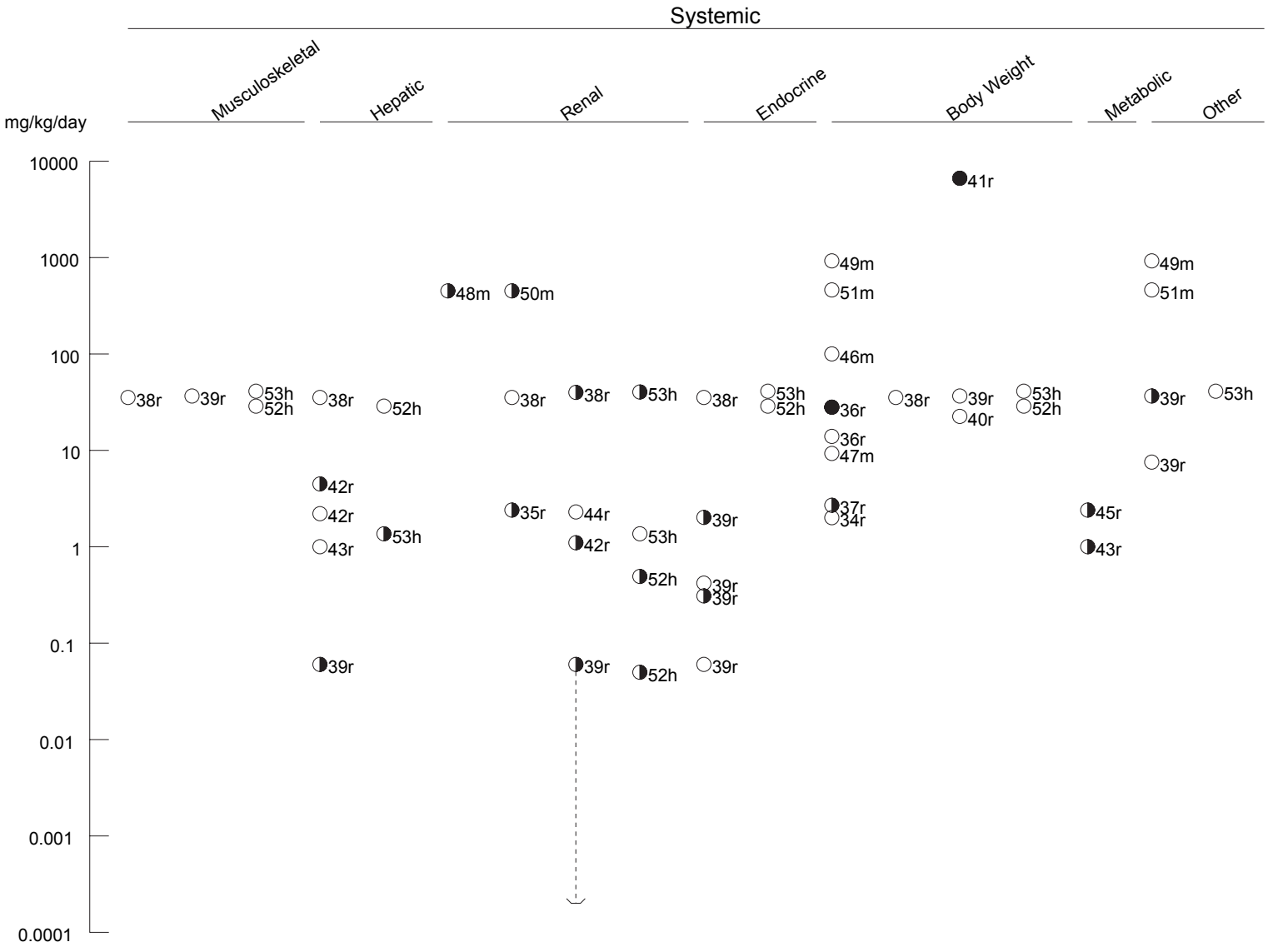
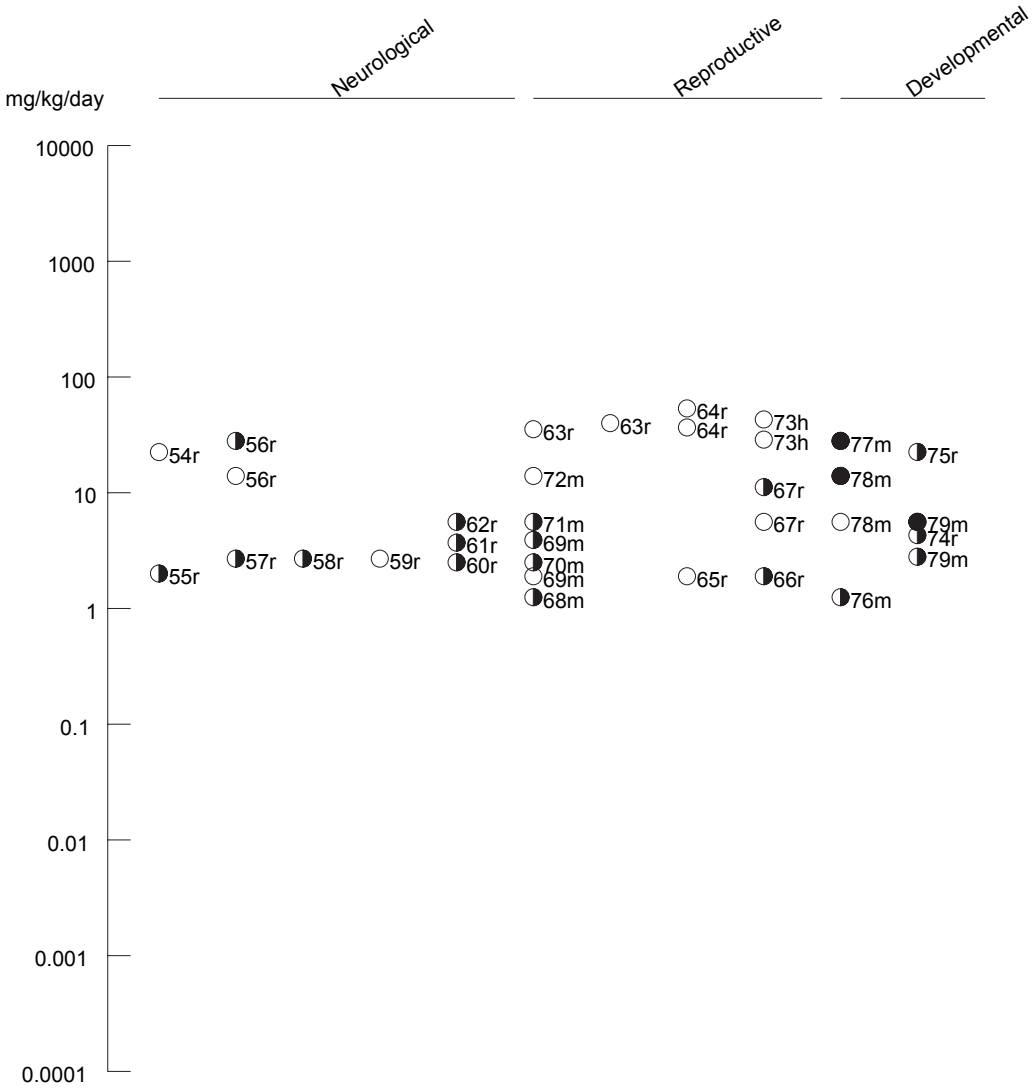


Figure 3-2 Levels of Significant Exposure to Uranium - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

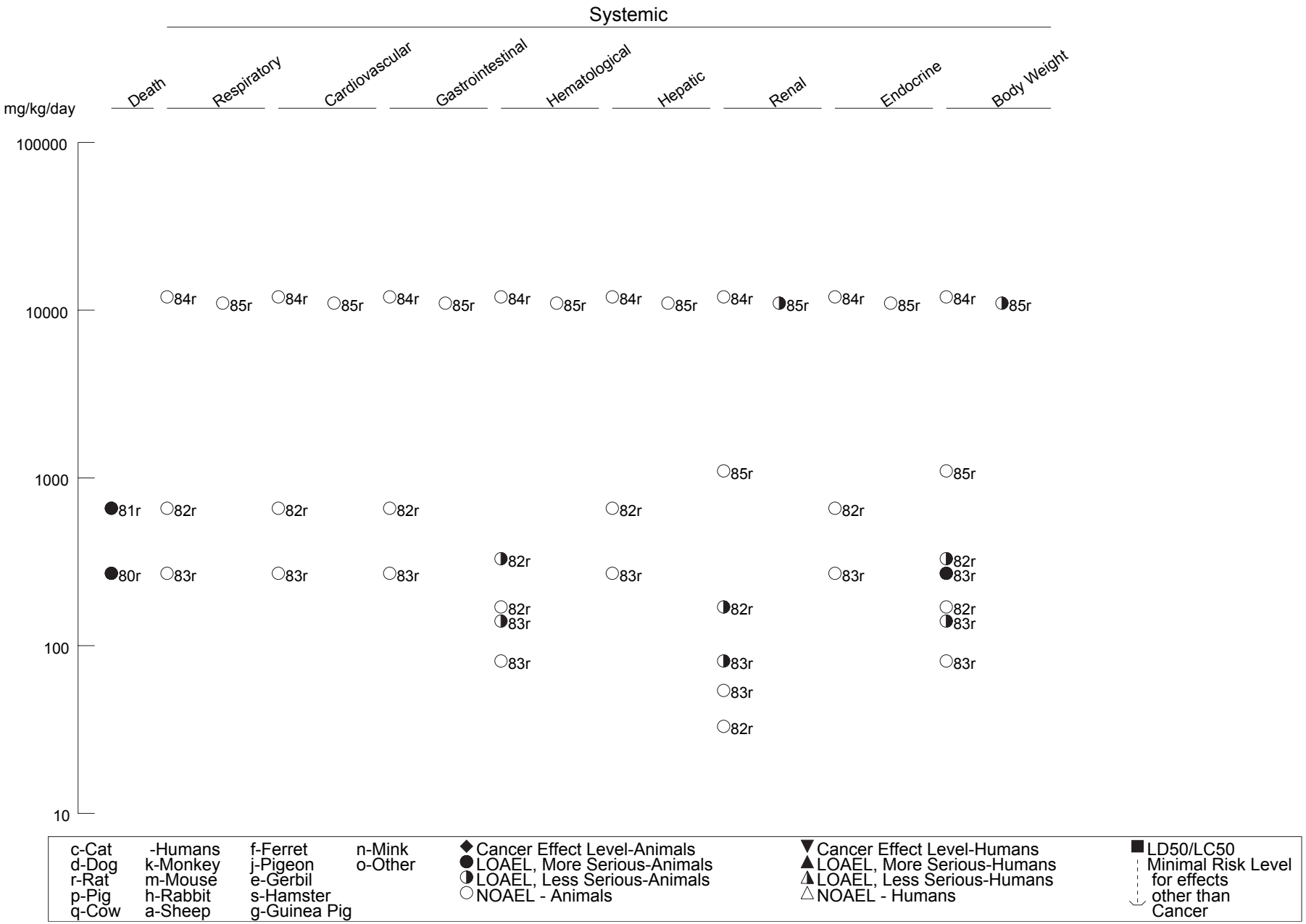
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-2 Levels of Significant Exposure to Uranium - Oral *(Continued)*

Chronic (≥365 days)



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/kg body weight/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 using much higher doses, 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).

No histological alterations were observed in the lungs of rats exposed to 400 mg U/kg/day as uranyl fluoride, 660 mg U/kg/day as uranyl nitrate, 11,000 mg U/kg/day as uranium tetrafluoride, or 12,000 mg U/kg/day as uranium dioxide in the diet for 2 years (Maynard and Hodge 1949; Maynard 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).

A significant association between urinary uranium levels and increases in diastolic and systolic blood pressure were observed among adults living in households with uranium in the drinking water at levels of 0.03–1,500 µg/L (31% >100 µg/L and 55% >15 µg/L; the median daily intake was 36 µg/day) (Kurttio et al. 2006a); however, the increases in blood pressure were small and did not appear until urine uranium levels were at least 1 µg/L. A urinary uranium level of 1 µg/L is approximately 25 times higher than the 95% percentile level for the U.S. population (CDC 2012). This is consistent with the findings of Kurttio et al. (2002) that a 1 mg/L increase in uranium levels in drinking water would be associated with 7.4 and 5.0 mm Hg increases in systolic and diastolic blood pressure, respectively. Kurttio et al. (2006a) noted that the increases in blood pressure were expectedly greater in older individuals than younger individuals.

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).

No histological alterations were observed in the heart of rats exposed to 400 mg U/kg/day as uranyl fluoride, 660 mg U/kg/day as uranyl nitrate, 11,000 mg U/kg/day as uranium tetrafluoride, or 12,000 mg U/kg/day as uranium dioxide in the diet for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

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: 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).

No histological alterations were observed in the stomach, small intestine, or large intestine of rats exposed to 400 mg U/kg/day as uranyl fluoride, 660 mg U/kg/day as uranyl nitrate, 11,000 mg U/kg/day as uranium tetrafluoride, or 12,000 mg U/kg/day as uranium dioxide in the diet for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

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 contrast, a 20% reduction in erythrocyte levels was observed in male Sprague-Dawley rats exposed to 2.4 mg U/kg/day as depleted uranyl nitrate hexahydrate in mineral water for 9 months (Berradi et al. 2008). The study did not find reductions in erythrocyte production in the spleen or bone marrow or evidence of alterations in spleen iron recycling. The investigators suggested that the observed hematological effect may be secondary to observed kidney damage.

In a 2-year feeding study, decreases in erythrocyte levels and/or hemoglobin levels were observed in rats exposed to ≥330 mg U/kg/day as uranyl nitrate or ≥140 mg U/kg/day as uranyl fluoride; an increase in

leukocyte levels was also observed at ≥140 mg U/kg/day as uranyl fluoride (Maynard and Hodge 1949; Maynard et al. 1953). No hematological alterations were observed in rats similarly exposed to 11,000 mg U/kg/day as uranium tetrafluoride or 12,000 mg U/kg/day as uranium dioxide (Maynard and Hodge 1949; Maynard et al. 1953).

Musculoskeletal Effects. In one human case report, a male (no age or weight given) was admitted to the 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 a study of adults (146 men and 142 women) living in an area of Finland with elevated uranium levels in drinking water (0.002–1,920 µg/L with 27% of concentrations >100 µg/L and 59% >15 µg/L), a significant association between elevated serum type I collagen carboxy-terminal telopeptide (CTx) levels (biomarker of bone resorption) and levels of uranium in water was observed in males (Kurttio et al. 2005). A nonsignificant association between increased osteocalcin levels (biomarker of bone formation) and uranium levels in drinking water was also observed in males. Other biomarkers of bone resorption and formation were not associated with uranium exposure. No statistically significant associations were observed in females. Daily uranium intakes ranged from 7 to 207 µg (0.0001–0.003 mg/kg/day, using a 70-kg reference body weight) and the median intake was 36 µg (0.0005 mg/kg/day).

There are limited data on the potential of uranium to induce bone or muscle damage following oral exposure. A significant decrease in growth cartilage width, metaphyseal bone volume, and percent metaphyseal activity in bone formation area and a significant increase in metaphyseal activity in the bone resorption area were observed in male Balb/c mice administered a single gavage dose of 170 mg U/kg as uranyl nitrate hexahydrate and sacrificed 48 hours after dosing (Bozal et al. 2005).

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 male (no age or weight given) was admitted to the 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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT). 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 was 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 in 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).

Significant increases in plasma cholesterol (41%) were observed in rats exposed to approximately 2 mg U/kg/day as depleted uranyl nitrate in drinking water for 9 months (Souidi et al. 2005); the toxicological significance of this increase is not known.

No histological alterations were observed in rats exposed via the diet for 2 years to 400 mg U/kg/day as uranyl fluoride, 660 mg U/kg/day as uranyl nitrate, 11,000 mg U/kg/day as uranium tetrafluoride, or 12,000 mg U/kg/day as uranium dioxide (Maynard and Hodge 1949; Maynard et al. 1953).

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. Few human data are available that adequately describe the dose-response toxicity of uranium after an oral exposure. In one human case report study (Pavlakis et al. 1996), acute nephrotoxicity was diagnosed in a male following the intentional ingestion of 15 g of uranyl acetate (approximately 131 mg/kg using a reference body weight of 70 kg), along with an unknown quantity of benzodiazepine, in a failed suicide attempt. 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; the patient underwent chelation therapy and dialysis. At 6 months following the initial toxic insult, the patient still suffered from an incomplete Fanconi syndrome (renal tubular acidosis). A pre-existing peptic ulcer disease in this patient may have exacerbated toxicity by increased absorption of uranium through the damaged stomach mucosal layer.

Several epidemiology studies (Kurttio et al. 2002, 2006a; Limson Zamora et al. 1998, 2009; Mao et al. 1995; Seldén et al. 2009) examined the possible association between chronic exposure to elevated levels of uranium in drinking water and alterations in kidney function. Mao et al. (1995) found a significant association between cumulative uranium exposure (product of uranium concentration in drinking water, reported average number of cups of water consumed per day, and the total years at the current residence) and urine albumin levels (expressed as mg/mmol creatinine) in adults living in households with elevated uranium levels in drinking water. The mean uranium levels in the drinking water were 19.6 and 14.7 µg/L in the exposed group and 0.71 µg/L in the control group. Although a significant association between cumulative uranium exposure and urinary albumin levels was found, the albumin levels were within the normal range for most subjects.

A significant association between uranium intake levels and urinary glucose, β_2-microglobulin, and alkaline phosphatase levels were observed in males and females living in an area of high uranium levels in the drinking water; total uranium intake ranged from 3 to 570 µg/kg (0.00004–0.0085 mg/kg/day, assuming a reference body weight of 70 kg) (Limson Zamora et al. 1998).

In a second study by this group (Limson Zamora et al. 2009), urine uranium levels (adjusted for fluid intake) were significant positively correlated with urine volume, specific gravity, γ-glutamyl transferase, and β2-microglobulin levels in a group of 54 residents exposed to various levels of uranium in drinking water. The estimated average uranium intake for the group was 0.00065 mg/kg/day; however, uranium intake was estimated from data for all subjects, which included eight subjects with a uranium intake of <0.0000013 mg/kg/day (1.3 ng/kg/day).

No significant differences in kidney function parameters were found in 301 residents consuming drinking water from wells drilled in bedrock areas and 153 consuming municipal water (Seldén et al. 2009). When the two populations were combined, urinary uranium levels were significantly correlated with β2-microglobulin, kappa immunoglobulin light chains, and protein HC levels; however, there was no dose-response relationship. Excluding 23 subjects with diabetes resulted in a tendency toward a dose-

response relationship. The median, mean, and range of uranium levels in the drinking water from wells were 6.7, 25.2, and <0.20–470 µg/L, respectively; the municipal water uranium levels were below the detection limit of 0.2 µg/L. The respective median and geometric mean urine uranium levels were 0.013 and 0.016 nmol/mmol creatinine in the well water group and 0.0019 and 0.0020 nmol/mmol creatinine in the municipal water group.

A weak significant association between urinary uranium levels and fractional excretion of calcium and phosphate were observed in 325 Finnish residents exposed to uranium in drinking water from bored wells (Kurttio et al. 2002); a tendency for increased glucose excretion was also observed. However, the lack of information on the presence of other possible contaminants in the drinking water confounds the interpretation of these results. The investigators noted that calcium, phosphate, and glucose excretion levels were within the normal range. Urinary uranium levels ranged from 1 to 5,650 µg/L (1.9–955 ng/mmol creatinine) and the mean and median levels were 424 and 78 µg/L (73 and 13 ng/mmol creatinine), respectively. The mean uranium intake was 3.2 mg/kg/day. No significant associations were found for β2-microglobulin levels or indicators of glomerular dysfunction (creatinine clearance or urinary albumin). Several years later, Kurttio et al. (2006a) examined a subset of these subjects (uranium drinking water levels ranged from 0.03 to 1,500 µg/L with 55% >15 µg/L and 31% >100 µg/L) and did not find significant associations between urinary uranium levels and calcium, phosphate, and glucose excretion. However, a significant association between cumulative uranium intake and urinary glucose levels was found.

There is sufficient information in animals with high exposures to both soluble and insoluble uranium to conclude that uranium is a renal toxicant. 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).

Two single exposure studies have reported renal damage. Marked increases in blood urea and creatinine levels and tubular necrosis were observed after 2 days in Balb-c mice administered a lethal (animals died on day 3) gavage dose of 166 mg U/kg as uranyl nitrate hexahydrate (Martinez et al. 2003). Evidence of renal dysfunction (increased urine volume, increased plasma urea and creatinine levels, and increased urinary total protein levels and creatinine clearance) and minimal microscopic lesions (moderate hyperemia and discrete microhemorrhagic foci) in the tubular epithelium were observed in male Sprague-Dawley rats exposed to a single gavage dose of 5.6 mg U/kg as uranyl acetate dihydrate (Domingo et al.

1987). In a repeated exposure acute-duration study, significant increases in BUN and serum creatinine levels were observed in Swiss albino mice exposed to 508 mg U/kg/day as uranyl acetate dihydrate in the diet for 5 days (Ozmen and Yurekli 1998).

The renal toxicity of uranium compounds following intermediate-duration exposure has been examined in rats, rabbits, and dogs (Gilman et al. 1998a, 1998b, 1998c; Maynard and Hodge 1949; McDonald-Taylor et al. 1992, 1997; Rouas et al. 2011). No histological alterations were observed in the kidneys of Sprague-Dawley rats exposed to doses as high as 35.3 mg U/kg/day (males) or 40.0 mg U/kg/day (females) as uranyl nitrate in drinking water for 28 days (Gilman et al. 1998a). 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). Similarly, no histological alterations were observed in Sprague-Dawley rats exposed to doses as high as 4.5 mg U/kg/day as uranyl acetate in drinking water for 4 weeks (Ortega et al. 1989a); small congestion of the kidney and a moderate increase in lysosomal content of the proximal convoluted tubule epithelial cells were observed at 9 mg U/kg/day. In addition, a slight, non-dose-related increase in total plasma protein levels was observed at ≥1.1 mg U/kg/day.

Extending the exposure duration to 91 days resulted in a number of kidney effects in Sprague-Dawley rats exposed to uranyl nitrate in drinking water (Gilman et al. 1998a). At the lowest dose tested in males (0.06 mg U/kg/day), histological alterations were observed in the renal tubules (nuclear vesiculation, cytoplasmic vacuolation, and tubular dilation) and interstitium (lymphoid cuffing). Exposure to ≥0.31 mg U/kg/day resulted in glomerular adhesions and tubular cytoplasmic degeneration. Although female rats were equally susceptible to the renal toxicity of uranyl nitrate, the observed histological alterations differed from the males. In the females exposed to ≥0.09 mg U/kg/day, capsular sclerosis, tubular anisokaryosis, tubular nuclear vesiculation, and interstitial reticulin sclerosis were observed. The differences in renal effects between the male and female rats do not appear to be related to uranium levels in the kidney. Although uranium levels were not measured at the lowest dose levels, exposure to 7.54 or 9.98 mg U/kg/day resulted in kidney uranium levels of 0.42 and 0.42 μg/g in males and females, respectively.

Gender-related differences in the renal toxicity of uranium were also observed in New Zealand rabbits exposed to uranyl nitrate in the drinking water for 91 days (Gilman et al. 1998b). Histopathological alterations observed in males exposed to ≥0.05 mg U/kg/day included cytoplasmic vacuolation, anisokaryosis, and nuclear vesiculation in proximal tubular cells. At the lowest dose tested in females (0.49 mg U/kg/day), anisokaryosis, nuclear vesiculation, and atrophy were observed in the proximal

tubules. At higher doses, interstitial reticulin sclerosis (0.88 and 1.32 mg U/kg/day in males and females) and interstitial collagen sclerosis (4.82 and 43.02 mg U/kg/day in males and females) were also observed.

In contrast to the results of this study, another 91-day study conducted by Gilman et al. (1998c) did not find statistically significant increases in the incidence of histological alterations in the kidneys of New Zealand rabbits exposed to 1.36 mg U/kg/day as uranyl nitrate in the drinking water for 91 days. Exposure to 40.98 mg U/kg/day resulted in increases in the incidence of cytoplasmic vacuolation, anisokaryosis, nuclear hyperchromicity, tubular dilation, tubular atrophy, and interstitial collagen and reticulum sclerosis. Most of these histological alterations persisted throughout a 91-day recovery period. Electron micrographic examination of the glomeruli and proximal tubules were conducted by McDonald-Taylor et al. (1992, 1997). A dose-related increase in the thickness of the glomerular basement membrane was observed in the 1.36 and 40.98 mg U/kg/day groups; as compared to the control group, the glomerular basement membranes were 20 and 36% thicker in the 1.36 and 40.98 mg U/kg/day groups, respectively (McDonald-Taylor et al. 1992). Observed effects in the proximal tubules included lumens filled with debris, a reduction in the height of epithelial cells, focal loss of brush border, splitting of the basal lamina, and renal interstitial fibrosis (McDonald-Taylor et al. 1997); these alterations were more common in the 40.98 mg U/kg/day group, but were also observed in some animals in the 1.36 mg U/kg/day group (incidence not reported). At the end of the 91-day recovery period, there was an increase in the thickness of the glomerular basement membrane and an increase in the severity of the proximal tubule lesions, as compared to values in rabbits sacrificed at the end of the exposure period (McDonald-Taylor et al. 1992, 1997). The results of this study (Gilman et al. 1998c) conflict with the results of this group's previous rabbit study (Gilman et al. 1998b). The investigators suggested that there were differences in the ways that animals in the two studies handled the ingested uranium and that the animals in the Gilman et al. (1998c) study more effectively cleared the uranium resulting in lower uranium levels in the kidney and bone. In this study (Gilman et al. 1998c), the uranium levels in the kidney and bone in rabbits ingesting a total intake of 3,557.25 mg U/kg/91 days were 3.48 and 2.89 μg/g, as compared to kidney and bone levels of 4.98 and 4.04 μg/g in rabbits ingesting 2,677.87 mg U/kg/91 days (Gilman et al. 1998b). Additionally, the investigators noted that some of the rabbits in the Gilman et al. (1998b) study were infected with *Pasteurella mutocida*; although animals with known infections were excluded from the study, some of the remaining rabbits may have had subclinical infections that may have affected their response to administered uranium.

In a longer exposure study, an increased incidence of tubule-interstitial lesions were observed in the kidneys of male Sprague-Dawley rats exposed to 2.4 mg U/kg/day as depleted uranyl nitrate hexahydrate

in mineral water for 9 months (Berradi et al. 2008). However, in a similar study, no alterations in the incidence of renal lesions were observed in rats administered 2.3 mg U/kg/day as depleted uranyl nitrate hexahydrate in drinking water for 9 months (Rouas et al. 2011).

Maynard and Hodge (1949) conducted a series of 30-day dietary exposure studies in rats and dogs using various uranium compounds. Although the results were poorly reported, the rat studies provide useful information for comparing the relative renal toxicity of different uranium compounds. No histological alterations were observed in the kidneys of rats exposed to 12,000 mg U/kg/day as uranium dioxide, uranium trioxide, or uranyl octaoxide or 11,000 mg U/kg/day as uranium tetrafluoride. Mild to moderate renal lesions were found in rats exposed to 440 mg U/kg/day as uranium tetrachloride (NOAEL of 90 mg U/kg/day) or 790 mg U/kg/day as uranium acetate (NOAEL of 200 mg U/kg/day). Mild histological alterations were observed in rats exposed to 200 mg U/kg/day as uranyl nitrate (NOAEL of 40 mg U/kg/day), 270 mg U/kg/day as uranyl fluoride (NOAEL of 140 mg U/kg/day), or 140 mg U/kg/day as uranium peroxide (NOAEL of 55 mg U/kg/day). The relative toxicity of the various uranium compounds were similar in the dog studies; however, the use of one dog per dose level limits the interpretative value of this study.

The chronic toxicity of uranium compounds was evaluated in a series of dietary exposure studies conducted by Maynard and associates (Maynard and Hodge 1949; Maynard et al. 1953) involving a 1-year exposure of dogs to uranium dioxide, uranyl fluoride, uranium tetrafluoride, uranium tetrachloride, or uranyl nitrate and a 2-year exposure of rats to uranium dioxide, uranyl fluoride, uranium tetrafluoride, or uranyl nitrate. A 2-year exposure of rats to uranyl fluoride or uranyl nitrate resulted in minimal tubular alterations at 81 and 170 mg U/kg/day, respectively; at higher doses (≥140 and ≥330 mg U/kg/day, respectively), the renal damage progressed to tubular atrophy (Maynard and Hodge 1949; Maynard et al. 1953). Exposure to the less soluble compound, uranium tetrafluoride, resulted in mild tubular degeneration at the highest dose tested (11,000 mg U/kg/day). No renal effects were observed in rats exposed to uranium dioxide at doses as high as 12,000 mg U/kg/day for 2 years. Although interpretation of the dog studies (Maynard and Hodge 1949; Maynard et al. 1953) is limited by the small number of dogs tested (typically two dogs per dose), the results are consistent with the chronic rat studies and with shorter duration studies. Soluble uranium compounds, such as uranyl nitrate and uranyl fluoride, were more toxic than less soluble or insoluble compounds. Renal tubular atrophy was observed in dogs exposed to 9.5 mg U/kg/day as uranyl nitrate, 7.7 mg U/kg/day as uranyl fluoride, 31 mg U/kg/day as uranium tetrachloride, 150 mg U/kg/day as uranium tetrafluoride, and 900 mg U/kg/day as uranium dioxide; the severity of the atrophy increased with dose.

The relationship between duration of exposure and the progression of renal lesions was evaluated in a serial exposure study in which rats were exposed to 33, 170, or 660 mg U/kg/day as uranyl nitrate hexahydrate in the diet (Maynard et al. 1953). At 660 mg U/kg/day, slight degeneration and necrosis were observed after 1 day of exposure; the extent and severity of the degeneration and necrosis continued to progress during the first week of exposure. At the end of the second week of exposure, there was less evidence of necrosis and more evidence of typical regeneration in the renal tubules. Tubular atrophy was observed in rats exposed for 6–10 weeks, which progressed in severity and extent over the next 18 weeks with a concomitant decrease in tubular regeneration. At 26 weeks, atrophy was the most prominent feature with dilation of atrophic tubules and narrowing of the cortex. At the end of the 1-year study, moderate to moderately severe tubular atrophy was observed. At the 170 mg U/kg/day dose, necrosis and degeneration were observed after 2 days of exposure and the severity continued to progress during the first week of exposure. After 2 weeks of exposure, regeneration of the tubular epithelium was the prominent effect. The severity of damage did not vary much during the first 30 weeks of exposure, with the exception of tubular atrophy detected in a small number of animals at 30 weeks. After 1 year of exposure, the renal alterations were primarily regeneration with slight atrophy in some animals. No uranium-related effects were observed in rats exposed to 33 mg U/kg/day. The results of this study suggest that at low doses, the tubular epithelium is regenerated and further exposure does not result in more severe effects. However, at higher doses, the capacity of the kidney to regenerate the damaged epithelium is exceeded, resulting in atrophy; continued exposure results in further damage to the kidney.

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, or 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.

No histological alterations were observed in the thyroid, adrenals, or pancreas of rats exposed to 400 mg U/kg/day as uranyl fluoride, 660 mg U/kg/day as uranyl nitrate, 11,000 mg U/kg/day as uranium tetrafluoride, or 12,000 mg U/kg/day as uranium dioxide in the diet for 2 years (Maynard and Hodge 1949; Maynard et al. 1953).

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 a result of reduction in food consumption due to distaste rather than of uranium-specific chemical or radiological toxicity. Similarly, uranium in drinking water may influence palatability (some investigators have added sugar to the water to increase palatability), which may result in decreased water consumption and possibly influence body weight.

In a 2-week drinking water study in rats, doses of 28 mg U/kg/day as depleted uranyl acetate dihydrate resulted in a 53% reduction in body weight gain in males; food consumption data were not provided (Briner and Murray 2005). In the same study, exposure for 6 months reduced body weight gain by approximately 46% in males and 36% in females; no significant effects were reported at 14 mg U/kg/day either in the 2-week or the 6-month experiments. In a developmental study in which rats were administered between 2.8 and 28 mg U/kg/day by gavage doses on gestation days 6–15, body weight gain during the treatment period was 33–88% lower than the control group (Domingo et al. 1989c); this was associated with significant reductions in food consumption. 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 et al. 1951), or 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). 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 et al. 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). In two more recent drinking water studies in rats, doses of approximately 2–2.7 mg U/kg/day as uranyl nitrate hexahydrate in mineral water for up to 9 months did not significantly affect body weight or food or water consumption (Bensoussan et al. 2009; Bussy et al. 2006). In mice, exposure via the drinking water to up to 100 mg U/kg/day as uranyl nitrate hexahydrate for 15 weeks had no significant effect on body weight (Arnault et al. 2008).

In series of chronic rat dietary studies (Maynard and Hodge 1949; Maynard et al. 1953), decreases in body weight gain were observed in rats exposed to 330 mg U/kg/day as uranyl nitrate, 140 mg U/kg/day as uranyl fluoride, and 11,000 mg U/kg/day as uranium tetrafluoride; no alterations in body weight gain were observed in rats exposed to 12,000 mg U/kg/day as uranium dioxide.

Metabolic Effects. Tissandié et al. (2006, 2007) found alterations in $1,25(OH)_2D_3$ (active form of vitamin D) levels in rats exposed to a single gavage dose of depleted uranyl nitrate or depleted uranyl nitrate in mineral water for 9 months. One day after gavage administration of 97 mg U/kg, a significant 62% increase in $1,25(OH)_2D_3$ level was observed in male Sprague-Dawley rats; 3 days after

administration, there was a significant decrease (68% compared to controls) in the level (Tissandié et al. 2006). Significant decreases in serum inorganic phosphate levels (15% at day 1 and 28% at day 3) and parathyroid hormone (day 3 only) levels (90%) were also observed. Intermediate-duration exposure to 2.4 mg U/kg/day also resulted in significant decreases in $1,25(OH)_2D_3$ levels; however, no alterations in $25(OH)D_3$ (vitamin D metabolite), plasma calcium, inorganic phosphate, parathyroid hormone, or osteoclacin levels were found (Tissandié et al. 2007). Alterations in mRNA expression levels of *cyp24a1* (encoding the enzyme that directs the catabolism of vitamin D) and vitamin D target genes involved in calcium homeostasis were also observed in the 9-month study.

3.2.2.3 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 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 mg U/kg/day; females: 53.56 mg U/kg/day). No lesions were observed in bone marrow, mesenteric and medistinal lymph nodes, or 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 et al. 1951). No other specific immunological tests were performed.

3.2.2.4 Neurological Effects

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

There is a limited number of reports of neurological effects in animals following acute oral exposure to uranium compounds. A study aimed at determining an oral LD_{50} for uranyl acetate dihydrate in Sprague-Dawley rats given single gavage doses ranging from 11 to 717 mg U/kg reported piloerection, tremors, hypothermia, pupillary size decreases, and exophthalmos (Domingo et al. 1987). The signs became more severe as the number of days posttreatment increased; however, the study did not specify the dose levels at which the various clinical signs appeared.

Two more recent acute-duration studies focused on the neurobehavioral effects of uranium and on effects on brain neurotransmitters. Administration of 28 mg U/kg/day (depleted uranyl acetate dihydrate) to Long-Evans rats via the drinking water for 2 weeks significantly increased motor activity in males as judged by number of lines crossed and rearing frequency, no significant effect was reported at 14 mg U/kg/day (Briner and Murray 2005); similar but nonsignificant alterations in open-field behavior were observed in females. Lipid oxidation in the brain was significantly increased in males and females dosed with 28 mg U/kg/day. According to the investigators, lines crossing and rearing frequency exhibited significant correlations with brain lipid oxidation, but the correlation coefficients were only 0.21 and 0.23, respectively, indicating that only about 4% of the variance in the behavioral tests could be explained by changes in lipid oxidation. Briner and Murray (2005) also exposed rats for 6 months to 14 or 28 mg U/kg/day and found increases in line crossing and rearing behavior in males at 14 and 29 mg U/kg/day and increased line crossing in females at 29 mg U/kg/day. However, lipid oxidation did not correlate with line crossing or rearing behavior. In a 2-week study in Swiss-Webster mice that also measured neurotransmitters and their metabolites in the midbrain, exposure to 6 mg U/kg/day (depleted uranyl acetate dihydrate; only dose level tested) significantly increased open-field line crossing in females, but not in males (Briner 2009). Exposure to uranium significantly increased tyrosine and decreased 3,4-dihydroxyphenylalanine (DOPA), norepinephrine (NE), and epinephrine (E); it had no significant effect on dopamine (DA) or homovanillic acid (HVA). According to the investigator, levels of DOPA in the midbrain were inversely related to lines crossed in open field (r^2=0.12). Exposure to uranium

significantly increased brain lipid oxidation, but lipid oxidation did not correlate with levels of tyrosine, DOPA, NE, E, or HVA.

Intermediate-duration oral studies that examined the gross and microscopic appearance of the brain of animals exposed to uranium have not reported compound-related alterations in male and female Sprague-Dawley rats exposed via drinking water to up to 40 mg U/kg/day as uranyl nitrate for 28 days or up to 54 mg U/kg/day for 91 days (Gilman et al. 1998a), and in male and female New Zealand rabbits similarly exposed to up to 43 mg U/kg/day for 91 days (Gilman et al. 1998b).

Intermediate-duration studies have also examined the effects of uranium on behavior, transmitter levels in the brain, including genes involved in neurotransmitter metabolism, and oxidative stress in the brain.

A study of neurotransmitter levels in the brain of male Sprague-Dawley rats following 1.5, 6, or 9 months of dosing with approximately 2.7 mg U/kg/day as depleted uranyl acetate dehydrate in mineral water; only dose level tested) reported that acetylcholinesterase activity was not significantly affected in the striatum, hippocampus, or frontal cortex at any time point, but it was significantly decreased in the cerebellum at 6 months (Bussy et al. 2006). Of many biochemical measurements conducted, the only significant changes were as follows: increased dopamine in the hypothalamus at 1.5 months, decreased ratio (3,4-dihydroxyphenylacetic acid [DOPAC]+HVA)/DA in the frontal cortex at 6 months, decreased 5HIAA and the ratio 5HIAA/5HT in the frontal cortex at 9 months, and decreased DOPAC and (DOPAC+HVA)/DA in the striatum at 9 months. Uranium significantly increased in the striatum at 1.5 months and to a lesser extent at 9 months (not measured at 6 months). Bensoussan et al. (2009) examined alterations in cholinergic system in response to a 1.5- or 9-month exposure to 2 mg U/kg/day as uranyl nitrate in mineral water. After 1.5 months of exposure, there were significant decreases in acetylcholine levels and acetylcholinesterase activity in the cortex; there were no alterations in the hippocampus. At 9 months, there was a decrease in acetylcholinesterase activity in the cortex, but no changes in acetylcholine levels, and no alterations in the hippocampus. Based on alterations in gene expression, the investigators noted that exposure to uranium seemed to induce transcriptional alterations in the hippocampus aimed at preserving acetylcholine levels, whereas in the cortex, exposure led mainly to translational alterations that increased acetylcholinesterase levels after 9 months of exposure. The investigators also noted that the lack of correlation between the increase in genes expressing cortical acetylcholinesterase and the decrease in acetylcholinesterase activity in the cortex could be explained by the complex relation between mRNA and enzyme activity.

A 3-month drinking water study in male Sprague-Dawley rats dosed with up to 22.4 mg U/kg/day (uranyl acetate dihydrate) that conducted behavioral tests including open-field activity, passive avoidance, and Morris water maze reported that exposure to uranium did not significantly affect any of the behavioral tests (Belles et al. 2005). A study that compared the effects of depleted and 4% enriched uranium (2.7 mg U/kg/day in mineral water for 1.5 months) in Sprague-Dawley rats reported that whole brain of controls had comparable amounts of uranium as brains of rats exposed to depleted or enriched uranium (Houpert et al. 2005). However, uranium was 1.5–2 times higher in the hypothalamus and hippocampus from rats dosed with enriched uranium than in control rats or rats exposed to depleted uranium. No significant increases in uranium levels were observed in the cortex, striatum, brainstem, or cerebellum were observed in the enriched or depleted uranium groups. Rats exposed to enriched uranium had a significant increase in the amount of paradoxical sleep (37%) compared to controls. In addition, exposure to enriched, but not depleted, uranium significantly decreased spatial working memory capacities and increased anxiety. In an additional study by the same group of investigators, male Sprague-Dawley rats exposed to 2.5 mg U/kg/day as 5.26% enriched uranyl nitrate for 9 months via drinking water (Houpert et al. 2007b). Four neurobehavioral tests (activity in open field, a two-object recognition task, a test for spatial working memory in a Y-maze, and a forced swimming test) were conducted before dosing started and at 3, 6, and 9 months. The only test that was affected by exposure to uranium was the spatial working memory test after 3 and 9 months of exposure, but not after 6 months. The investigators suggested that the results may indicate that enriched uranium disrupts memory in a spatial task involving the hippocampus but does not affect memory in another task in which hippocampal functioning is less crucial.

In a study examining the effects of uranium on the sleep cycle, Sprague-Dawley rats were exposed to uranium in drinking water for 90 days. An increase in the amount of time spent in rapid eye movement (REM) sleep was observed in rats exposed to 3.7 mg U/kg/day as 4.92% enriched uranyl nitrate in mineral water for 30 or 60 days; a nonsignificant increase was observed after 90 days of exposure (Lestaevel et al. 2005b). This increase in REM sleep was due to the number of REM sleep episodes rather than an increase in the duration of REM episodes. The increases in the amount of REM sleep primarily occurred during the light period (normal sleeping period for rats), suggesting that the circadian rhythms were not affected by uranium exposure.

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

3.2.2.5 Reproductive Effects

No human studies were located regarding reproductive effects following oral exposure to uranium compounds.

Some animal studies, mostly in rodents, have shown effects on some aspects of male and female reproductive function following exposure to uranium. For the most part, general toxicity studies that conducted gross and microscopic examination of the reproductive organs did not report adverse effects. For example, no histopathology or changes in reproductive organ weight were reported in Sprague-Dawley rats 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). 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 (Maynard et al. 1953).

Fertility has been assessed in a few studies. Fertility was not significantly affected in a study in which male Swiss mice were given gavage doses of up to 14 mg U/kg/day as uranyl acetate dihydrate for 60 days before mating with females that had received the same doses for 14 days (Paternain et al. 1989). In a 64-day drinking-water study with Swiss-Webster mice, treatment of males with ≥5.6 mg U/kg/day (uranyl acetate) followed by mating with untreated females resulted in significant reductions in pregnancy rates, which were associated with significant reductions in spermatozoa counts and reduced epididymal weights (Llobet et al. 1991). Treatment of male Sprague-Dawley rats with 11.2 mg U/kg/day (uranyl acetate) in the drinking water for 3 months before mating with untreated females also resulted in a significant reduction in pregnancy rate; no significant effect was reported at 5.6 mg U/kg/day (Linares et al. 2005). In this study, there were no significant effects on the number of total implants/litter or number of viable and nonviable implants/litter. Neither the absolute nor relative weight of the testes and epididymis was significantly affected; a significant decrease in the number of spermatid/testis was observed at ≥11.2 mg U/kg/day. Microscopic examination of the testes showed a progressive, but not significant, loss of Sertoli cells or germinal cells with cytoplasmic vacuolization. Maynard and associates

conducted two continuous breeding studies to evaluate the effect of uranium on fertility. In the first study (Maynard and Hodge 1949), pairs of male and female rats were exposed to 2% uranyl nitrate hexahydrate in the diet for 200 days (650 and 750 mg U/kg/day in males and females, respectively) followed by 5 months on the control diet. A dramatic decrease in the number of litters produced (46%) was observed in the uranium-exposed group; a decrease in the average number of offspring per litter was also observed. Irregular estrous cycles were observed in 14/44 of the uranium-exposed rats compared to 2/45 controls. The investigators suggested that the decreased fertility and irregular estrous cycle may have resulted from the marked decrease in body weight (after 200 days of exposure, the uranium group weighed 23% less than controls) and decreased food intake (no data provided). In the second study (Maynard et al. 1953), pairs of male and female weaning rats were administered 2% uranyl nitrate hexahydrate in the diet for 24 hours (1400 mg U/kg/day) and then fed a stock diet for 1 year. A slight decrease (7%) in the total number of litters was observed in the uranium group; a 12% decrease in the total number of offspring was also observed. No alterations in body weight gain were observed. Interpretation of the study results to evaluate whether uranium affects reproduction (in the absence of marked decreases in body weight gain) is difficult because the Maynard et al. (1953) study did not conduct a statistical analysis of the data to determine whether the small decreases in number of litters and litter size were significant.

The effects of uranium on ovarian function have also been studied. Exposure of female C57Bl x CBA mice to ≥1.25 mg U/kg/day (uranyl nitrate hexahydrate) in drinking water for 15 weeks resulted in slight disturbance in ovarian folliculogenesis (Arnault et al. 2008). In a similar study, exposure of female Swiss mice to up to 10 mg U/kg/day (uranyl nitrate hexahydrate) for 40 days in drinking water did not alter the mean number of oocytes ovulated per female (Kundt et al. 2009). However, doses of ≥2.5 mg U/kg/day significantly increased (more than doubled) the percentage of dysmorphic oocytes; the increases consisted of increases in perivitaline space at ≥5 mg U/kg/day, lysed oocytes at 2.5 and 5 mg U/kg/day, fragmented oocytes at 10 mg U/kg/day, and nonspherical oocytes at ≥2.5 mg U/kg/day. Exposure to uranium also significantly increased the incidence of micronuclei in cumulus cells (oocyte-supporting cells); a strong correlation between the number of micronuclei and dose was found. The mitotic index in cumulus cells was significantly decreased in the mid- and high-dose groups in a dose-related fashion. Uranium also increased the number of metaphase plate abnormalities in oocytes arrested in metaphase II. In yet another study, exposure of hybrid female mice to up to 6.9 mg U/kg/day (uranyl nitrate hexahydrate) for 49 days in drinking water did not affect the number of ovulated oocytes (Feugier et al. 2008). Oocyte quality was not affected by the lowest dose tested (1.9 mg U/kg/day), but the proportion of healthy oocytes was reduced by half at doses ≥3.9 mg U/kg/day. Absence of the first polar body and abnormal perivitaline space were the main morphological alterations. An increase from the 3.9 to 6.9 mg U/kg/day dose did not

increase the proportion of oocytes with abnormalities, but led to a diversification in oocyte abnormalities. Both Arnault et al. (2008) and Feugier et al. (2008) measured uranium in the ovaries and reported no significant accumulation of the chemical. Effects of uranium on ovarian folliculogenesis were also studied by Raymond-Whish et al. (2007). Administration of approximately 0.08 or 0.39 mg U/kg/day as depleted uranyl nitrate hexahydrate to 28-day-old B6C3F1 mice in tap water for 30 days significantly decreased the number of large primary follicles in the ovary, whereas a larger dose of 1.9 mg U/kg/day increased secondary or growing follicles. No significant alterations were observed at 9.3 mg U/kg/day. In a different experiment, female mice were exposed to much smaller doses (0.00008–0.009 mg U/kg/day) of uranium for 30 days prior to mating with untreated males and then continued to be dosed during gestation. Necropsy of dams on postnatal day 5 showed that doses ≥0.00039 mg U/kg/day significantly reduced the number of small primary follicles; however, all other follicle populations including primordial, secondary/growing, healthy, and atretic were unchanged.

Raymond-Whish et al. (2007) also examined the potential estrogenic properties of uranium. Exposure of ovariectomized (at 28-days of age) mice to 0.009 mg U/kg/day as depleted uranyl nitrate hexahydrate for 30 days significantly increased proliferation of the epithelial cell lining of the uterus, and uterus weight increased 3-fold; however, significant effects were not observed at 0.09 or 0.9 mg U/kg/day. In addition, mice exposed to 0.005 and 0.009 mg U/kg/day had significantly increased presence of cornified vaginal cells, indicative of estrogenic effects of uranium. In a similar experiment, exposure of ovariectomized C57Bl/6J mice to 0.005 mg U/kg/day for 10 days beginning at 50 days of age significantly increased uterine weight and exposure to 0.009 mg U/kg/day significantly accelerated vaginal opening; both effects were blocked by intraperitoneal injections of an antiestrogenic drug. These effects were observed at doses that are several orders of magnitude lower than the adverse effect levels of other studies and were not observed at higher uranium doses. Additional research is needed to confirm these results; thus, the LOAEL values are not presented in Table 3-2 or plotted in Figure 3-2.

A study was conducted to distinguish chemical versus radiological effects of uranium on the metabolism of steroids in rat testes (Grignard et al. 2008). Sprague-Dawley rats were exposed to 0 or 1.9 mg depleted or 4.24% enriched U/kg/day (uranyl nitrate hexahydrate) in the drinking water for 9 months. Exposure to depleted uranium did not significantly affect blood levels of testosterone or 17β-estradiol. Exposure to depleted uranium also did not significantly affect the levels of genes encoding proteins regulating steroid synthesis. In addition, depleted uranium did not significantly alter the expression levels of transcription factors regulating the expression of the genes that were monitored. Exposure to enriched uranium did not significantly affect blood levels of 17β-estradiol, but significantly increased testosterone levels and the

expression of genes involved in steroidogenesis. In addition, enriched uranium significantly increased the expression of transcription factors involved in the regulation of steroidogenic genes. These results led the investigators to suggest that the adverse effects were mainly due to the radiological activity of the compounds.

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 3-2 and plotted in Figure 3-2.

3.2.2.6 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.

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, or 28 mg U/kg/day from gestation day 13 through postnatal day 21 (Domingo et al. 1989b). 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 milestones (pinnae unfolding, lower incisor eruption, eye opening) or in pup weight or body length. Structural variations were not assessed in this report. Two dams in the 2.8 mg U/kg/day group and three in the 28 mg U/kg/day group died during the last period of gestation. Although the cause of death was not determined, it was attributed to the administration of uranium. Yet, the investigators stated that maternal toxicity was not evident from changes in body weight and/or food consumption.

Increased late resorptions and decreased live fetuses were reported in Swiss mice administered 14 mg U/kg/day (uranyl acetate dihydrate) by gavage for 14 days before mating with males that received the same doses for 60 days; the females were sacrificed on gestation day 13 (Paternain et al. 1989). No significant effects were reported at 5.6 mg U/kg/day. In dams that were allowed to give birth and nurse the offspring until 21 days of age (dams' exposure continued during gestation and lactation), doses of 5.6 mg U/kg/day significantly increased neonatal death per litter, and the lowest dose tested, 2.8 mg

U/kg/day, significantly reduced pup weight on postnatal day 21 (Paternain et al. 1989). No information was provided in this study regarding maternal effects. Dose-related fetotoxicity, manifested as reduced fetal body weight and length, increased incidence of stunted fetuses and external and skeletal malformations, and increased incidence of developmental variations were reported in the offspring of 20 pregnant Swiss mice given uranyl acetate dihydrate (2.8, 5.6, 14, and 28 mg U/kg/day) by gavage on gestation days 6–15 and sacrificed on gestation day 18 (Domingo et al. 1989c). A significant increase in the number of external defects was observed at ≥2.8 mg U/kg/day. The external malformations included a significant increase in the incidence of cleft palate (≥5.6 mg U/kg/day) and hematomas (at 2.8 and 28 mg U/kg/day). A significant increase in the incidence of skeletal abnormalities (bipartite sternebrae and reduced or delayed ossification of the hindlimb, forelimb, skull, and tail) was seen in the 14 and 28 mg U/kg/day groups. Embryolethality was not found at any of the dose levels tested. Maternal toxicity was evident in all treated groups, as a dose-related significant reduction in maternal weight gain during exposure occurred (43% reduction in the lowest dose group, 82% in the highest dose group); this may have played a role in the observed developmental effects.

More recent studies also provide information on the developmental effects of uranium. Exposure of female Sprague-Dawley rats to doses of 0, 22.5, or 45 mg U/kg/day (uranyl acetate dihydrate) in the drinking water for 4 weeks before mating with untreated males and continued dosing during gestation and lactation had no significant effect on pup developmental landmarks such as pinna detachment, incisor eruption, and eye opening (Sánchez et al. 2006). Neuromotor maturation was also not affected, but passive avoidance acquisition and retention time 24 hours after the test were significantly modified. The lowest dose tested significantly reduced pup body weight on postnatal day 21, but not on postnatal day 1. The only maternal effects reported in this study were a significant dose-related increase in body weight gain on gestation days 0–14 and a significant increase in gravid uterine weight at 45 mg U/kg/day; no data were provided regarding food consumption. Neurodevelopment was also examined by Houpert et al. (2007a) in offspring from Sprague-Dawley rats exposed to 0 or approximately 4.3 mg U/kg/day as 4.24% enriched uranyl nitrate hexahydrate in mineral water for 3 months before mating and during gestation and lactation. Behavioral tests were performed in male offspring at 2, 5, and 9 months. Rats were tested for locomotor activity and rearing indices, a spatial working memory test, and an elevated plus-maze test. At 2 months, when the tests began, exposed pups were comparable to control pups in body weight and organ weight (brain, kidneys, femur, and skull). Uranium did not accumulate in the brain. The results of the motor and behavioral tests showed that exposure to uranium induced hyperactivity in the offspring at 5 months and was more evident at 9 months; the investigators considered this to be delayed hyperactivity. This was evidenced by increased rearing indices and activity in the open field (not statistically

significant), and increased activity in the two mazes. The results also showed a reversible slight decrease in spatial working memory. The only information regarding the dams in this study was that body weight gain during gestation was comparable between treated and control groups.

Two studies reported effects on ovarian folliculogenesis in female offspring from exposed mice. Arnault et al. (2008) exposed C57Bl x CBA mice to 0, 1.25, 12.5, or 100 mg U/kg/day (uranyl nitrate hexahydrate) in the drinking water for 15 weeks. Mice were then mated to untreated males, and dams and female pups were sacrificed 3 months later. Microscopic examination of the ovaries of the female pups showed that pups from exposed dams had a significantly decreased percentage of the largest follicles. The investigators noted that the effect could be due either to a direct effect of transplacental transfer of uranium or to an indirect effect resulting from uranium-induced physiological disturbances in the dams, or both. In the other study, B6C3F1 mice were exposed via the tap water to low uranium doses ranging from approximately 0.00008 to 0.00093 mg U/kg/day as depleted uranyl nitrate hexahydrate for 30 days prior to breeding with untreated males (Raymond-Whish et al. 2007); treatment continued during gestation. In female pups, sacrificed on postnatal day 5, exposure to 0.00008 or 0.00093 mg U/kg/day significantly reduced primordial follicles. Nonsignificant decreases in primordial follicles were observed at 0.00039 and 0.00019 mg U/kg/day. The investigators noted that neonatal mouse ovaries only have oogonia and primordial follicles. These results in pups are analogous to the results in mouse dams, not-mated mice, and immature mice.

A study is available that examined the effect of a high dose of uranium on tooth eruption and development in young Wistar rats (Pujadas Bigi et al. 2003). One- or 7-day-old rats were administered a single gavage dose of 0 or approximately 42.7 mg U/kg (uranyl nitrate hexahydrate) in water and were sacrificed on days 7 or 14, respectively. Hemimandibles were resected and processed for microscopic examination. Bone formation was significantly reduced in the bucal and lingual aspects of 7-day-old treated rats. Bone resorption was significantly higher in the occlusal and lingual aspects of both 1- and 7-day-old treated rats. Tooth eruption was significantly lower in both treated groups compared with controls. Tooth development was also found to be significantly diminished in both treated groups compared with controls. The investigators suggested that the delay in tooth eruption may be due to decreased bone formation in the developing alveolar bone. They further speculated that the diminished tooth development may be caused by a toxic effect on Hertwig's sheath cells, odontoblasts, and cementoblasts. In a more recent study, the investigators showed that the delay in tooth eruption, dental development, and mandibular growth observed 7 days postdosing with uranium was no longer evident after day 27 (Pujadas Bigi and Ubios 2007).

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 3-2 and plotted in Figure 3-2.

3.2.2.7 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 a cancer bioassay, 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).

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/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).

There are limited data on the carcinogenicity of uranium compounds in animals. Chronic oral exposure studies in rats and dogs have not reported neoplasms following ingestion of several uranium compounds (Maynard and Hodge 1949; Maynard et al. 1953). The highest doses tested in 1-year dog studies were 95 mg U/kg/day as uranyl nitrate, 8 mg/kg/day as uranyl fluoride, 31 mg U/kg/day as uranium tetrachloride, 3,790 mg U/kg/day as uranium tetrafluoride, and 8,815 mg U/kg/day as uranium dioxide. In the rat 1-year studies, the highest doses tested were 664 mg U/kg/day as uranyl nitrate, 10,611 mg U/kg/day as uranium tetrafluoride, and 12,341 mg U/kg/day as uranium dioxide.

3.2.3 Dermal Exposure

3.2.3.1 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 5–7 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).

Decreased survival was observed in female Wistar rats following dermal application of 280 mg U as uranyl nitrate hexahydrate diluted in an oil-water emulsion; survival was inversely related to the duration of exposure and the application area (Lopez et al. 2000). A 24-hour application to 0.5, 1, 2, 4, 6, 8, or 16 cm^2 area resulted in survival rates of 80, 83, 67, 29, 33, 0, and 0%, respectively; application to 8 cm^2 for 1 minute, 7 minutes, 15 minutes, 30 minutes, 1 hour, 8 hours, or 24 hours resulted in survival rates of 100, 100, 100, 67, 45, 43, 10, and 0%, respectively.

Chemically induced renal failure caused 100% mortality in male Wistar rats after five 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/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 3-3.

3.2.3.2 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, hepatic, or endocrine effects of uranium in animals following acute-, intermediate-, or chronic-duration exposure. The existing animal data on musculoskeletal, renal, dermal, and body weight effects are limited to acute- and intermediate-duration exposures.

Table 3-3 Levels of Significant Exposure to Uranium - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
ACUTE EXPOSURE							
Death							
Rat (Wistar)	1-11 d 1x/d				1965 M mg/kg (60% mortality in 11 days)	De Rey et al. 1983 Uranyl Acetate	
Rat (Wistar)	1-11 d 1x/d				1928 M mg/kg (100% mortality in 5 days)	De Rey et al. 1983 Ammonium Uranyl Tricarbonate	
Rat (Wistar)	1-11 d 1x/d				237 M mg/kg (100% mortality in 5 days)	De Rey et al. 1983 Uranyl Nitrate	
Rat (Wistar)	4 hr (EPICU)				101 F mg/kg (LD50)	Orcutt 1949 Uranyl Nitrate	
Mouse (albino)	4 hr (EPICU)				4286 F mg/kg (LD50)	Orcutt 1949 Uranyl Nitrate	
Gn Pig	4 hr (EPICU)				2520 mg/kg (LD50)	Orcutt 1949 Uranium Tetrachloride	
Gn Pig (NS)	once (EPICU)				1190 mg/kg (LD50)	Orcutt 1949 Uranyl Nitrate	
Rabbit (New Zealand)	4 hr (EPICU)				188 mg/kg (50% mortality)	Orcutt 1949 Uranium Tetrachloride	

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rabbit (New Zealand white,red,chec	4 hr (EPICU)				3091 mg/kg (83% mortality)	Orcutt 1949 Uranyl Fluoride	
Rabbit (New Zealand)	4 hr (EPICU)				28 mg/kg (LD50)	Orcutt 1949 Uranyl Nitrate	
Rabbit (New Zealand)	once 4 hr (EPICU)				198 mg/kg (33% mortality)	Orcutt 1949 Ammonium Diuranate	
Rabbit (New Zealand)	4 hr (EPICU)				344 mg/kg (67% mortality)	Orcutt 1949 UCl5	
Rabbit (New Zealand)	4 hr (EPICU)				666 mg/kg (67% mortality)	Orcutt 1949 Uranium Trioxide	
Systemic							
Rat (Wistar)	1-11 d 1x/d	Renal			237 M mg/kg (renal failure)	De Rey et al. 1983 Uranyl Nitrate	
		Dermal		237 M mg/kg (mild lesion)			

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rat (Wistar)	1-11 d 1x/d	Dermal	1928 M mg/kg			De Rey et al. 1983 Ammonium Uranyl Tricarbonate	
		Bd Wt		1928 M mg/kg (slight initial weight loss)			
Rat (Wistar)	1-11 d 1x/d	Renal			1965 M mg/kg (renal failure)	De Rey et al. 1983 Uranyl Acetate	
		Dermal	3929 M mg/kg				
		Bd Wt			1965 M mg/kg (70% weight loss)		
Rat (Wistar)	1-11 d 1x/d	Renal			2670 M mg/kg (renal failure)	De Rey et al. 1983 Ammonium Diuranate	
		Dermal		2670 M mg/kg (mild lesions)			
		Bd Wt			2670 M mg/kg (severe weight loss)		

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rat (Wistar)	once (EPICU)	Renal		85 F mg/kg	(proteinuria; minimal microscopic lesions in renal tubular epithelium)		Orcutt 1949 Uranyl Nitrate	
		Bd Wt		85 F mg/kg	(unspecified decreased body weight gain)			
Mouse (albino)	4 hr (EPICU)	Renal		948 F mg/kg	(moderate tubular degeneration)		Orcutt 1949 Uranyl Nitrate	
		Bd Wt		948 mg/kg	(unspecified decreased body weight gain)			
Gn Pig (NS)	4 hr (EPICU)	Renal		660 mg/kg	(proteinurea)		Orcutt 1949 Uranium Tetrachloride	
		Bd Wt		660 mg/kg	(10-20% reduction in weight gain)			
Gn Pig (NS)	4 hr (EPICU)	Renal	450 mg/kg	616 mg/kg	(proteinuria)		Orcutt 1949 Uranyl Nitrate	
		Bd Wt	450 mg/kg	616 mg/kg	(unspecified decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Gn Pig (NS)	4 hr (EPICU)	Renal		689 mg/kg	(proteinuria)		Orcutt 1949 Uranium Tetrachloride	
		Bd Wt		689 mg/kg	(10-20% decreased bod weight gain)			
Rabbit (New Zealand)	4 hr (EPICU)	Renal	410 mg/kg				Orcutt 1949 Uranium Peroxide	
		Dermal	410 mg/kg					
Rabbit (New Zealand)	4 hr (EPICU)	Renal	458 mg/kg				Orcutt 1949 Uranium Dioxide	
		Dermal	458 mg/kg					
Rabbit (New Zealand)	4 hr (EPICU)	Renal	98 mg/kg				Orcutt 1949 Uranium Tetrafluoride	
		Dermal	98 mg/kg					

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rabbit (New Zealand)	4 hr (EPICU)	Renal		195 mg/kg (proteinuria)		Orcutt 1949 Sodium Uranate	
		Dermal	195 mg/kg				
Rabbit (New Zealand)	4 hr (EPICU)	Renal		666 mg/kg (proteinuria)		Orcutt 1949 Uranium Trioxide	
		Dermal	666 mg/kg				
Rabbit (New Zealand)	4 hr (EPICU)	Renal	147 mg/kg			Orcutt 1949 Triuranium Octoxide	
		Dermal	147 mg/kg				
Rabbit (New Zealand)	4 hr (EPICU)	Renal		344.1 mg/kg (proteinuria)		Orcutt 1949 UCl5	
		Dermal		344.1 mg/kg (moderate skin irritation)			

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
Rabbit (New Zealand)	once (EPICU)	Renal		618 mg/kg	(proteinuria)			Orcutt 1949 Uranyl Fluoride	
		Dermal	618 mg/kg						
Rabbit (New Zealand)	4 hr (EPICU)	Renal		1.4 mg/kg	(proteinuria)			Orcutt 1949 Uranyl Nitrate	
		Dermal		1.4 mg/kg	(moderate erythema)				
		Bd Wt	6 mg/kg	30 mg/kg	(decreased body weight gain)				
Rabbit (New Zealand)	4 hr (EPICU)	Renal		169 mg/kg	(proteinuria)			Orcutt 1949 Ammonium Diuranate	
		Dermal	169 mg/kg						
INTERMEDIATE EXPOSURE									
Death									
Gn Pig (NS)	4 wk 3 d/wk					47 mg/kg	(12% mortality)	Orcutt 1949 Uranyl Nitrate	

Table 3-3 Levels of Significant Exposure to Uranium - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
Gn Pig (NS)	4 wk 3 d/wk					379 mg/kg	(14% mortality)	Orcutt 1949 Uranyl Nitrate	
Systemic									
Gn Pig (NS)	4 wk 3-6 d/wk	Renal		47 mg/kg/day	(proteinuria)			Orcutt 1949 Uranyl Nitrate	
		Dermal		47 mg/kg/day	(skin irritation)				
		Bd Wt	47 mg/kg/day	161.2 mg/kg/day	(transitory weight loss)				
Rabbit (New Zealand)	5 wk 5 d/wk	Renal		2.3 mg/kg/day	(proteinuria)			Orcutt 1949 Uranyl Nitrate	
		Dermal				2.3 mg/kg/day	(severe dermal ulcers)		
		Bd Wt		2.3 mg/kg/day	(temporary weight loss)				

Bd Wt = body weight; d = day(s); Gn Pig = guinea pig; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

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 3-3.

Musculoskeletal Effects. Statistically significant decreases in bone volumes were observed in female Wistar rats following an application of 280 mg U as uranyl nitrate hexahydrate diluted in an oil-water emulsion to a 1 or 2 cm^2 area for 24 hours or an 8 cm^2 area for 24 hours, but not after 30 minutes, 1 hour, or 8 hours (Lopez et al. 2000).

Renal Effects. Vascular congestion and vacuolization of the tubules in the corticomedullary boundary were observed in female Wistar rats following a 1–30-minute application of 280 mg U as uranyl nitrate hexahydrate diluted in an oil-water emulsion to an 8 cm^2 area or following 24 hours of exposure to uranyl nitrate applied to a 0.5 or 1 cm^2 area (Lopez et al. 2000). Application of uranyl nitrate to an 8 cm^2 area for 1–24 hours or to a 2–16 cm^2 area for 24 hours resulted in formation of hyaline bodies and necrosis. 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 >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). Kidney lesions were also observed in female Wistar rats dermally exposed to 600 mg uranyl nitrate hexahydrate in an oil-water emulsion; the severity of the renal lesions increased with increasing exposure durations or increasing amount of exposed skin (Lopez et al. 2000). Chemically induced renal failure caused 100% mortality in male Wistar rats after five 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. Although no human studies were located regarding the dermal effects of uranium; no dermal effects were reported in studies of uranium miners, millers, and processors exposed to airborne uranium.

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).

3.2.3.3 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.

3.2.3.4 Neurological Effects

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

In animal studies, neurological signs including irritability, hyperactivity, upset equilibrium, limb rigidity, and respiratory arrest were observed in rabbits exposed to lethal doses of uranyl nitrate hexahydrate (Orcutt 1949); decreases in food and water intake and body weight were also observed in these animals.

3.2.3.5 Reproductive Effects

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

3.2.3.6 Developmental Effects

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

3.2.3.7 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.

3.2.4 Other Routes of Exposure

Embedded/Implanted Uranium

A cohort of Gulf War I veterans exposed to depleted uranium were initially examined in 1994 (Hooper et al. 1999) and re-examined every 2 years beginning in 1997 (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b). Over the years, additional soldiers with embedded metal fragments have been added to the original cohort. The veterans were in or on armored tanks and fighting vehicles when they were fired upon by other U.S. forces using depleted uranium penetrators. These veterans may have been exposed to depleted uranium via inhalation, ingestion, fragment penetration wounds, and wound exposure to dust; some of the soldiers who were injured were left with multiple tiny fragments of uranium and other substances in muscle and/or soft tissue. However, not all of the embedded fragments contained depleted uranium (Squibb et al. 2012). In a study of excised fragments from two veterans, no fragments contained depleted uranium; the fragments were primarily composed of copper, lead, iron, and zinc (Squibb et al. 2012). Urinary uranium levels have been consistently elevated in the veterans with embedded depleted uranium fragments. Urine uranium levels in the entire cohort ranged from 0.001 to 60 µg/g creatinine (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b); however, urinary uranium levels in the veterans with depleted uranium fragments were typically >0.1 µg/g creatinine. In comparison, the geometric mean urine uranium levels in the U.S. males (National Health and Nutrition Examination Surveys [NHANES] sampling periods of 1999–2008) ranged from 0.005 to 0.008 µg/g creatinine (CDC 2012) and the 95th percentile values ranged from 0.026 to 0.040 µg/g creatinine. A number of parameters were examined to evaluate potential adverse health effects associated with exposure to depleted uranium; potential targets included renal function, liver effects, hematological alterations, neuroendocrine hormone levels, semen characteristics, bone function, neurocogntive effects, and genotoxicity. The effect of uranium exposure on these parameters was examined by dividing the veterans into two groups: low exposure (urine uranium levels of <0.1 µg/g creatinine) and high exposure (urine uranium levels of ≥0.1 µg/g creatinine). The results of these studies for each end point are discussed in the following sections. Epidemiology studies of other war veterans exposed to depleted

uranium and animal studies involving exposure to uranium from implanted uranium are also discussed in the following sections.

Hematological Effects. As summarized in Table 3-4, no consistent alterations in hematological parameters were found in the Gulf War veterans (Hooper et al. 1999; McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b).

Potential hematological effects were observed in male and female Sprague-Dawley rats implanted with 20 1x2 mm pellets of depleted uranium in the gastrocnemius muscle for up to 150 days. A significant increase in the percentage of monocytes and decrease in platelet levels were observed, as compared to sham surgery controls (Arfsten et al. 2007). However, when a group of rats with implanted tantalum pellets was used as the control, no significant hematological alterations were observed.

Musculoskeletal Effects. The two most recent studies of the Gulf War veterans cohort (McDiarmid et al. 2009, 2011b) examined biomarkers of bone turnover and bone metabolism. A nonsignificant decrease in bone-specific serum alkaline phosphatase levels (measure of osteoblast function) was observed in the veterans with embedded fragments; however, no alteration in *N*-telopeptide levels (biomarker of collagen breakdown and bone resorption) was found (McDiarmid et al. 2009). The investigators suggested that the increase in osteoblast activity without an alteration in osteoclast activity may be a clinically insignificant uncoupling of the bone turnover process. A significant increase in 1,25-dihydroxy vitamin D levels was observed in the veterans with embedded fragments; the increased 1,25-dihydroxy vitamin D levels were within the normal range. The increase in 1,25-dihydroxy vitamin D levels, in the absence of changes in parathyroid hormone levels, may be a due to an alteration in renal function rather than an alteration in bone metabolism. In the most recent study, no significant alterations in bone biomarkers were found (McDiarmid et al. 2011b).

Decreased tibia growth and impaired mandibular growth were observed in female Wistar rats administered 110 mg U/kg as uranium dioxide implanted directly into the subcutaneous tissue of dorsal skin for 30 days (Díaz Sylvester et al. 2002). The decrease in bone growth was probably related to a marked decrease in active osteoblasts, which were replaced with a large increase in bone lining cells.

Table 3-4. Summary of Significant Observations in Studies of a Cohort of Gulf War Veterans Exposed to Depleted Uranium[a]

	Evaluation year							
Clinical parameter	1994[b]	1997[c]	1999[d]	2001[e]	2003[f]	2005[g]	2007[h]	2009[i]
Renal function								
Urine creatinine	NS	NS	l>h (p=0.07)	NS	NS	NS	NS	NS
Creatinine clearance	–	–	–	–	–	NS	NS	NS
Glomerular filtration rate	–	–	–	–	–		NS	NS
Urine glucose	–	–	–	–	–	NS	NS	NS
Urine calcium	–	–	–	NS	NS	NS	NS	NS
Urine phosphate	–	–	–	NS	NS	NS	NS	NS
Urine β2-microglobulin	NS	NS	NS	NS	NS	NS	h>l (p=0.11)	NS
Urine intestinal alkaline phosphatase	–	–	NS	NS	NS	NS	NS	NS
Urine NAG	–	–	NS	NS	NS	NS	NS	NS
Urine total protein	NS	NS	NS	h>l (p=0.06)	l>h (p=0.21)	NS	NS	NS
Urine microalbumin	–	–	–	–	NS	NS	NS	NS
Retinol binding protein	–	NS	NS	h>l (p=0.06)	h>l NS	NS	h>l (p=0.07)	NS
Serum creatinine	NS	NS	NS	L>H	NS	NS	NS	L>H
Serum calcium	NS	NS	H>L	NS	NS	NS	NS	NS
Serum phosphate	NS	NS	NS	NS	H>L	NS	NS	NS
Serum uric acid	NS	NS	NS	NS	NS	NS	NS	NS
Serum chemistry								
Alanine aminotransferase	NS	NS	NS	NS	NS	NS	NS	NS
Aspartate aminotransferase	NS	NS	NS	NS	h>l NS	NS	NS	NS
Lactate dehydrogenase	NS	NS	L>H	L>H	NS	NS	NS	NS
Alkaline phosphatase	NS	NS	NS	NS	NS	NS	NS	NS
Hematological parameters								
Hematocrit	NS	NS	NS	L>H	NS	NS	NS	NS
Hemoglobin	NS	NS	NS	L>H	NS	NS	NS	NS
White blood cells	H>L	NS	NS	NS	NS	NS	NS	NS
Lymphocytes	L>H	NS	L>H	NS	NS	NS	NS	NS
Neutrophils	H>L	NS	H>L	NS	NS	NS	NS	NS
Basophils	NS	NS	NS	NS	NS	NS	NS	NS
Eosinophils	NS	H>L	NS	NS	NS	NS	NS	NS
Monocytes	L>H	NS	L>H	NS	NS	NS	NS	NS
Platelets	NS	NS	NS	NS	NS	NS	NS	NS

Table 3-4. Summary of Significant Observations in Studies of a Cohort of Gulf War Veterans Exposed to Depleted Uranium[a]

	Evaluation year							
Clinical parameter	1994[b]	1997[c]	1999[d]	2001[e]	2003[f]	2005[g]	2007[h]	2009[i]
Bone markers								
Estradiol	–	–	–	–	–	–	NS	
Bone specific-alkaline phosphatase	–	–	–	–	–	–	NS	NS
1,25-Dihydroxy vitamin D	–	–	–	–	–	–	H>L	NS
25-Hydroxy vitamin D	–	–	–	–	–	–	NS	NS
Parathyroid hormone	–	–	–	–	–	–	NS	NS
Urine N-teleopeptide	–	–	–	–	–	–	NS	NS
Neuroendocrine hormones								
Follicle stimulating hormone	–	NS	NS	NS	NS	NS	NS	NS
Luteinizing hormone	–	NS	NS	l>h (p=0.06)	NS	NS	NS	NS
Testosterone	–	NS	NS	NS	NS	NS	NS	NS
Thyroid stimulating hormone	–	–	NS	NS	NS	NS	NS	NS
Free thyroxine	–	–	NS	L>H	NS	NS	NS	NS
Semen characteristics								
Semen volume	–	NS	NS	NS	NS	NS	NS	
Sperm concentration	–	H>L	h>l (p=0.09)	h>l NS	h>l NS	NS	NS	
Total sperm count	–	NS	H>L	h>l (p=0.06)	h>l NS	NS	NS	
Percent motile sperm	–	NS	NS	NS	NS	NS	NS	
Total progressive sperm	–	NS	H>L	NS	NS	NS	NS	
Percent progressive sperm	–	NS	NS	NS	NS	NS	NS	
Total rapid progressive sperm	–	NS	H>L	NS	NS	NS	NS	
Percent rapid progressive sperm	–	NS	NS	NS	NS	NS	NS	

[a]Table modified from Squibb and McDiarmid (2006); lower case letters indicate nonsignificant findings; upper case letters indicate significant findings ($p<0.05$).
[b]Hooper et al. 1999.
[c]McDiarmid et al. 2000.
[d]McDiarmid et al. 2001a.
[e]McDiarmid et al. 2004b.
[f]McDiarmid et al. 2006.
[g]McDiarmid et al. 2007.
[h]McDiarmid et al. 2009.
[i]McDiarmid et al. 2011b.

h,H = high urine uranium (≥0.1 µg/g creatinine); l, L = low urine uranium group (<0.1 µg/g creatinine); NAG = *N*-acetyl-β-glucosaminidase; NS = not significant; – not determined

Hepatic Effects. There are limited data on the potential hepatotoxicity of embedded depleted uranium; no consistent alterations in several clinical chemistry parameters (ALT, AST, lactate dehydrogenase, alkaline phosphatase) were found in Gulf War veterans (Hooper et al. 1999; McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b).

Renal Effects. In general, no significant alterations in parameters of kidney function were observed among Gulf War veterans (Hooper et al. 1999; McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b); a summary of these data are presented in Table 3-4. However, the increases in several parameters, including urinary retinol binding protein and β-2-microglobulin levels approached statistical significance in the veterans with embedded fragments. No alterations in *N*-acetyl-β-glucosaminidase levels (a biomarker of renal proximal tubule cell cytotoxicity) were found (McDiarmid et al. 2009, 2011b). Of the biomarkers of renal function, only urine retinol binding protein and β-2-microglobulin levels were in the direction that would be indicative of renal damage (McDiarmid et al. 2009), and retinol binding protein levels were altered at several examination periods. During the period of 2001–2009, increases in retinol binding protein excretion were observed in the high exposure group at three of the four examinations. Urine retinol binding protein levels at the 2001, 2003, 2007, and 2009 examinations were 46.13, 27.33, 31.00, and 28.49 µg/g creatinine in the low exposure group and 65.68, 80.51, 48.11, and 40.12 µg/g creatinine in the high exposure group. The difference between the two groups did not reach statistical significance and the levels are within the normal range (<610 µg/g creatinine, McDiarmid et al. 2009). Although the difference was not statistically significant and values were within the normal range, there is concern (Squibb and McDiarmid 2006) because retinol binding protein may be a potential sentinel marker of proximal tubular effects from uranium.

Alterations in renal function and histopathology were observed in rats 90, 180, or 360 days after 0.1, 0.2, or 0.3 g of depleted uranium fragments (each 8x2x1 mm weighing 0.1 g) were embedded in the gastrocnemius muscle (Zhu et al. 2009b). Rats in each group were implanted with 0 fragments (sham surgery controls), 1 depleted uranium and 2 tantalum fragments, 2 depleted uranium and 1 tantalum fragment, 3 depleted uranium fragments, or 3 tantalum fragments. The histological alterations included swollen glomeruli with infiltrated inflammatory cells, turgidity and epithelial necrosis in the tubules, and interstitial fibrosis (360 days after fragment implantation). Significant increases in urinary β_2-microglobulin levels were observed in the 0.3 g group 180 and 360 days after implantation, and an increase in urinary albumin levels was observed in the 0.3 g group after 90 days (but not after the longer exposure durations); however, there were large standard deviations for these measurements.

Additionally, significant increases in serum creatinine levels were observed in all three exposed groups at 90 days, in the 0.3 g group at 180 days, and in the 0.2 and 0.3 g groups at 360 days; BUN levels were significantly increased in the 0.3 g group at 90 days and 0.2 and 0.3 g groups at 360 days (no significant alterations were observed at 180 days). Another study by this group also found significant decreases in 1-α-hydroxylase activity (responsible for the hydroxylation of $25(OH)D_3$ to $1\alpha,25(OH)_2D_3$ the active form of vitamin D) in the kidneys of rats exposed to 0.2 or 0.3 g depleted uranium embedded in the gastrocnemius muscle for 3 months (Yan et al. 2010); no significant alterations were observed at 6 or 12 months or in the 1 g group at any time period.

Endocrine Effects. As summarized in Table 3-4, no consistent alterations in neuroendocrine hormone levels have been found in the Gulf War veterans with embedded uranium (Hooper et al. 1999; McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b).

Body Weight Effects. Significant decreases in body weight gain were observed in rats 90 days following implantation of 0.1, 0.2, or 0.3 g of depleted uranium fragments (each 8x2x1 mm weighing 0.1 g) in the gastrocnemius muscle (see discussion of study methods in Renal Effects section) (Zhu et al. 2009b); the exposed rats weighed 11–21% less than controls with 0.3 g of biologically inert tantalum (Ta) fragments embedded in the gastrocnemius. One year after implantation, decreases in body weight gain (10–11%) were only observed in the 0.2 and 0.3 g groups.

A 25% decrease body weight gain was also observed in rats following implantation of 110 mg U/kg/day as uranium dioxide into the subcutaneous tissue of the dorsal skin for 30 days (Díaz Sylvester et al. 2002).

Neurological Effects. The results of neurocognitive tests in the Gulf War veterans cohort have not found significant differences between the high and low exposure groups (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011b). Significant associations between urine uranium levels and accuracy scores on neurocognitive tests were observed at several examinations; however, this association was strongly influenced by two subjects with extremely high uranium levels and severely complex co-morbid conditions due to combat injuries.

An animal study examined the effects of implanted depleted uranium alloy pellets on neurobehavior in adult rats (Arfsten et al. 2007). Groups of Sprague-Dawley rats (18–84 males and 17–42 females per group) were implanted with 1x2 mm pellets of depleted uranium in the gastrocnemius muscle for up to 150 days. Males received 12 or 20 pellets and females received 4, 8, 12, or 20 pellets. Controls were

implanted with 12 or 20 tantalum pellets. Beginning on postimplantation day 150, a portion of males and females were evaluated for spontaneous locomotor activity in an open field, acoustic startle/prepulse inhibition, and conspecific social approach. The results of the behavioral testing did not show definite evidence of neurobehavioral perturbations associated with depleted uranium implantation.

In another study of rats with implanted depleted uranium pellets, 4, 10, or 20 pellets were implanted in the gastrocnemius muscle for 6, 12, or 18 months (Pellmar et al. 1999b). Neurophysiological changes (impairment of ability of the synaptic potential to elicit the population spike, EPSP/spike coupling) were detected in the hippocampus 6 or 12 months after implantation; no effects were observed after 18 months, which may have been due to the effect of aging.

Reproductive/Developmental Effects. In the studies of the Gulf War veterans cohort (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009), differences in semen quality have been observed at a number of examinations (data summarized in Table 3-4); however, these data suggest improved quality in the high exposure group. No significant alterations were found for follicle stimulating hormone, luteinizing hormone, or testosterone. Although prolactin levels were elevated in the 1997 cohort, no differences were found in later evaluations.

The reproductive/developmental effects of implanted depleted uranium pellets have been studied in rats (Arfsten et al. 2006, 2009). Groups of Sprague-Dawley rats (6–18/sex/group) were implanted with 0, 4, 8, 12, or 20 depleted uranium pellets (1x2 mm) in the gastrocnemius muscle. Inert implant controls were implanted with 12 or 20 Ta pellets; sham-operated controls were also used. Urine was collected from F0 rats on day 27 and 117 for uranium analysis. Rats were mated on postimplantation day 120. Body weight of pregnant females was checked throughout pregnancy. F0 males were kept until necropsy on postnatal day 200. The pups were counted and weighed immediately after birth; sex ratio was also determined; pups were also examined for gross malformations during postnatal days 1–20. F0 females that did not deliver a litter were kept until necropsy on postnatal day 200. On postnatal day 2, F0 females and their offspring underwent maternal retrieval testing. On postnatal day 4, litters were culled to eight pups (four/sex); discarded pups were killed and the whole carcasses were analyzed for uranium. The remaining pups were kept with their mothers through postnatal day 20. On postnatal day 20, two pups/sex were killed and used for whole-body uranium analysis, gross examination of all major organs, and examination of the ribcage. Subsets of F1 pups underwent neurobehavioral testing on postnatal days 4–63. These tests assess developmental markers for basic proprioceptive coordination, social bonding, social interaction, and the developmental milestone of eye opening. F0 dams were necropsied

on postnatal day 200. Survival and body weight of F1 pups were monitored until postnatal day 120. On postnatal day 120, F0 and F1 males were killed and sperm motility and concentration were examined. Major organs of males and females were examined and weighed. The F2 generation was produced by mating F1 males with F1 females on postnatal day 70. F2 pups were subjected to the same tests as F1 except the maternal retrieval test. F1 males and females were killed on postnatal day 120. One male and one female per F2 litter were killed on postnatal day 90.

No clinical signs of toxicity were seen in F0 rats during the postimplantation period. Three male and 4 female F0 rats died during the study, but necropsy did not show an obvious cause of death. Depleted uranium had no significant effect on mating index. There were no significant differences among the groups regarding gestational index, gestation duration, or gestation weight gain. Viability of F1 pups to postnatal days 4 and 20 was similar across groups. Pup body weight gain during postnatal days 4–20 also was similar across groups. In F1 pups sacrificed on postnatal day 20, there were no gross abnormalities in the major organs and no alterations in the ribcage. Results of the neurobehavioral tests showed no significant depleted uranium-related effects. Evaluation of sperm parameters in F0 males on postnatal day 200 did not show compound-related effects. Histological examination of major organs from controls and rats implanted with 20 depleted uranium pellets and 20 Ta pellets only showed tissue reactions to the foreign body; neither depleted uranium nor Ta pellet implantation sites showed evidence of proliferative of preneoplastic processes taking place in or around the site. Body weight gain and body weight of F1 pups during postnatal days 20–120 were comparable among all groups. Eight of 414 F1 rats died before necropsy on postnatal day 120 of unknown causes. No gross abnormalities were seen in the remaining F1 rats. There did not seem to be compound-related effects on F1 organ weights or in histology of kidneys, spleen, thymus, bone marrow, ovaries, and testes. An increase in mean relative heart weight was observed in the highest dose F1 females, when compared to the sham-operated controls; however, there was no change in absolute heart weight and no difference in absolute or relative heart weight when compared to the inert pellet control group. Neither sperm motility nor concentration was significantly affected by depleted uranium in male F1 rats on postnatal day 120. Overall mating success of F1 rats was lower than F0 rats, but was comparable among all groups. No significant developmental effects were reported in F2 pups at birth or during postnatal days 0–20. Gross necropsy of F2 pups on postnatal day 20 showed no significant alterations; examination of the ribcage also showed no abnormalities. Necropsy of F2 rats on postnatal day 90 did not show consistent depleted uranium-related effects on organ weights; an increase in relative heart weight was observed in the highest dosed F2 males, but there was no change in absolute heart weight. Sperm motility parameters and sperm concentration were not significantly different among F2 groups.

A study was conducted in mice to determine whether paternal exposure to uranium could result in genetic damage to the offspring (Miller et al. 2010). The authors used a transgenic mouse system that employs a λ shuttle vector that allows mutations to be analyzed *in vitro*. Transgenic male mice were implanted with depleted uranium pellets (two, four, or six pellets) in the gastrocnemius muscle for 7 months and were then mated with untreated non-transgenic females to produce the F1 generation. Controls received implants of biologically inert tantalum. Litters from depleted uranium-implanted fathers were smaller in a dose-dependent manner than un-implanted or tantalum-implanted fathers. Paternal exposure to depleted uranium did not result in fetal malformations and no significant increase in offspring hematopoietic malignancies in weaned offspring was observed. At the age of 4–5 months, deoxyribonucleic acid (DNA) from bone marrow cells from F1 mice was screened for mutations. A significantly higher mutation frequency relative to controls was observed in mid- and high-dose F1 mice, comparable to the frequency seen in offspring of male mice exposed to 4 Gy of ^{60}Co gamma radiation delivered at 0.06 Gy/minute. Since the depleted uranium would have delivered a much lower radiation dose than the ^{60}Co, the comparable results are supportive of uranium effects being primarily chemical in nature.

Cancer. A study of Danish military personnel deployed to the Balkans between 1992 and 2001 (most were deployed for at least 6 months) did not find significant increases in the risk of all cancers or a specific type of cancer (Storm et al. 2006).

The carcinogenicity of implanted depleted uranium was studied in rats (Hahn et al. 2002). Groups of male Wistar rats (50/group) were implanted in the thigh muscle with fragments of depleted uranium (alloyed with 0.75% titanium) of two different sizes (2.5x2.5x1 mm or 5.0x5.0x1.5 mm) or a pellet (2.0x1 mm) for life. A negative control group was implanted with Ta; a positive control group received an intramuscular injection of radioactive thorium dioxide (ThO_2). Depleted uranium and Ta implants were encapsulated with connective tissue at the time of death. The capsules around depleted uranium were characterized histologically by fibrosis, inflammation, degeneration, and mineralization. All implants (depleted uranium, ThO_2, or Ta) had soft tissue tumors associated with the implants. The most prevalent was malignant fibrous histiocytoma, which was significantly increased in the high-dose depleted uranium fragment rats (5.0x5.0x1.5 mm) and in the positive control. There was no increase in tumors related to depleted uranium in tissues not associated with implant sites. The results showed that depleted uranium fragments of sufficient size cause localized proliferative reactions and soft tissue sarcomas that can be detected with radiography.

A significant increase in the incidence of leukemia was observed within 210 days of surgically implanting 6 depleted uranium pellets in the gastrocnemius muscle (3 pellets per leg) of DBA/2 mice, as compared to controls with or without Ta implants (Miller et al. 2005). In another experiment in which mice were implanted with 2, 6, or 8 depleted uranium pellets and 6, 2, or 0 tantalum pellets for 60 days followed by an intravenous injection of FDC-P1 hematopoietic cells, a dose-related increase in the incidence of leukemia was observed (Miller et al. 2005).

3.3 GENOTOXICITY

Prospective evaluations of Gulf War veterans with retained depleted uranium metal fragments have provided inconsistent results (Bakhmutsky et al. 2011; McDiarmid et al. 2000, 2001a, 2004b, 2007, 2009, 2011a). Tests have been conducted in peripheral blood lymphocytes and included evaluations of sister chromatid exchanges (SCEs), chromosomal aberrations (traditional measures as well as those identified through fluorescent *in situ* hybridization [FISH]), micronuclei frequency, hypoxanthine-guanine phosphoribosyl transferase (HPRT) mutation frequency, and phosphatidylinositol glycan class-A (PIG-A) gene mutant frequency. No significant alterations in chromosomal aberrations were found when veterans with higher urine uranium levels were compared with veterans with lower urinary uranium levels (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009, 2011a), although a nonsignificant increase in chromosome aberrations, as measured by FISH, was found at one of the examination periods (McDiarmid et al. 2007). Assessment of SCEs yielded inconsistent results as a function of urinary uranium levels; higher levels of SCEs were found in the low uranium group at two of the examination periods (McDiarmid et al. 2000, 2004a), higher levels were found in the high uranium group at one period (McDiarmid et al. 2004b), and no differences were found at another examination period (McDiarmid et al. 2006). Nonsignificant increases in HPRT mutation frequencies were observed higher in the high uranium group at three examination periods (McDiarmid et al. 2004b, 2006, 2007); however, at the last two examinations, there were no differences between the high and low groups (McDiarmid et al. 2009, 2011a). A nonsignificant increase in PIG-A mutant frequency was observed in the high exposure group at the last examination period (McDiarmid et al. 2011a). No significant alterations in the frequency of micronuclei were found between the two groups (Bakhmutsky et al. 2011; McDiarmid et al. 2011a). McDiarmid et al. (2009, 2011a) concluded that, overall, the body of evidence in this cohort shows relatively weak genotoxic effects from exposure to uranium.

Schröder et al. (2003) examined 16 war veteran volunteers suspected of exposures to depleted uranium. Since a control group subjected to the same multiple-agent exposures except for depleted uranium was

not available, the investigators chose subjects from their own laboratory as controls. Compared to the controls, there was a statistically significant increase in the frequency of dicentric chromosomes and centric ring chromosomes among veterans; SCEs were not increased. The results suggested previous exposure to ionizing radiation, but the different sources of exposure could not be ascertained. Four additional small studies from individuals in the former Republic of Yugoslavia who were exposed to depleted uranium either via consumption of contaminated food and/or clean-up operations reported increased frequencies of chromosomal aberrations in peripheral blood cells from the exposed subjects compared with unexposed controls (Krunić et al. 2005; Milačić 2008; Milačić and Simić 2009; Milačić et al. 2004). A cytogenic study of men occupationally exposed to uranium in a fuel production plant and in a fuel enrichment plant found higher levels of chromosome aberrations in the exposed workers than in controls (Martin et al. 1991). However, the possible role of smoking could not be assessed with certainty.

In an early animal study, male BALB/c mice injected intraperitoneally with doses ranging from 0.05 to 1.0 µg U/kg as 18.9% enriched uranyl fluoride showed a general tendency for an increase in chromosome breaks in sperm cells with an increasing dose of 18.9% 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). More recently, Monleau et al. (2006a) exposed male Sprague-Dawley rats nose-only to an aerosol of uranium dioxide at concentrations of 0, 190 mg/m^3 (0.5 hours), or 375 mg/m^3 (2 and 3 hours) and examined DNA damage in epithelial nasal cells, broncho-alveolar lavage cells (BAL), and kidney cells at various times postexposure. Groups of rats were also exposed repeatedly for 3 weeks to depleted uranium dioxide (190 mg/m^3; insoluble depleted uranium) and to uranium peroxide (116 mg/m^3; soluble depleted uranium) for 0.5 hours. No DNA damage occurred in nasal epithelial cells under any exposure scenario. BAL cells from rats exposed to 375 mg/m^3 uranium dioxide for 3 hours showed significant DNA damage 1 and 8, but not 3, days postexposure. A single 0.5-hour exposure to uranium peroxide did cause DNA damage in BAL cells. Repeated exposure to 190 mg/m^3 uranium dioxide produced DNA damage in BAL cells assessed 1, 4, 8, or 14 days postexposure. Kidney cells showed DNA damage only after repeated exposures to uranium dioxide. DNA damage consisted partly of double strand breaks, suggesting that radiation could be a contributor to the effects. These results suggested that there may be a threshold for effects of single exposure on BAL cells and that repeated inhalation exposure seemed to potentiate the effect of uranium in BAL and kidney cells. Since uranium exposure also increased the expression of cytokines involved in inflammatory responses in lung tissue and of peroxides, the investigators suggested that DNA damage may have been partly a consequence of inflammatory processes and production of reactive oxygen species. Another study from the same group of investigators reported that repeated exposure to uranium dioxide increased

the genotoxic effects of uranium peroxide inhalation in all three types of cells examined, when a single exposure to uranium peroxide had no significant effect (Monleau et al. 2006b). The investigators suggested that pre-exposure to insoluble uranium could slightly disturb the biokinetics of subsequently inhaled soluble uranium in the kidneys, gastrointestinal tract, and excreta.

In another study, groups of male and female Wistar rats were fed a diet that provided 0, 4, or 40 mg U/kg/day (depleted uranyl nitrate hexahydrate) for 4 months, at which time they were mated to produce the F1 generation (Hao et al. 2009). The offspring were treated in the same manner for 4 months. Exposure to uranium induced a statistically significant dose-related increase in the incidence of micronuclei in bone marrow from both the parental and F1 generations. It also induced DNA damage in the sperm from both generations in a dose-related manner. The effects were more pronounced in the F1 generation than in the parental groups. Analyses of uranium in urine and kidneys after the 4-month exposure period showed dose-related accumulation in the kidney, significantly higher in the F1 than in the parental generation. Hao et al. (2009) did not elaborate as to why the effects were more pronounced in the F1 generation than in the parental rats. One possible explanation could be that the F1 generation also could have been exposed during preweaning via the maternal milk.

A study was conducted in mice to determine whether paternal exposure to uranium could result in genetic damage to the offspring (Miller et al. 2010). The authors used a transgenic mouse system that employs a λ shuttle vector that allows mutations to be analyzed *in vitro*. Transgenic male mice were implanted with depleted uranium pellets (two, four, or six pellets) in the gastrocnemius muscle for 7 months and were then mated with untreated females to produce the F1 generation. At the age of 4–5 months, DNA from bone marrow cells from F1 mice was screened for mutations. A significantly higher mutation frequency relative to controls was observed in mid- and high-dose F1 mice, comparable to the frequency seen in offspring of male mice exposed to ^{60}Co gamma radiation. To assess the role of radiation in the observed effects of depleted uranium, male mice were exposed to equal concentrations of depleted or enriched uranium in the drinking water (approximately 1 mg U/mouse) for 2 months. Exposure to either form of uranium significantly increased the frequency of mutations compared with controls and also suggested that the increase was specific-activity dependent. While this experiment showed that radiation can play a role in the observed effects of depleted uranium, the investigators noted that the mutation model used measures point mutations and cannot measure large deletions characteristic of radiation damage, the role of the chemical effects of depleted uranium may also be significant.

Table 3-5 presents results of genotoxicity tests conducted *in vivo*.

Table 3-5. Genotoxicity of Uranium *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference
Mammalian systems:				
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Inhalation	+	Schröder et al. 2003
Human peripheral lymphocytes (DU)	Sister chromatid exchange	Inhalation	–	Schröder et al. 2003
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Oral	+	Milačić et al. 2004
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Inhalation	+	Milačić 2008
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Inhalation	+	Milačić and Simić 2009
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Inhalation	+	Krunić et al. 2005
Human peripheral lymphocytes	Chromosomal aberrations	Inhalation	+	Martin et al. 1991
Human peripheral lymphocytes	Sister chromatid exchange	Inhalation	+	Martin et al. 1991
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Retained metal fragment	+	McDiarmid et al. 2004a
Human peripheral lymphocytes (DU)	Chromosomal aberrations	Retained metal fragment	–	McDiarmid et al. 2000, 2001a, 2006, 2007, 2009, 2011a
Human peripheral lymphocytes (DU)	Sister chromatid exchange	Retained metal fragment	+	McDiarmid et al. 2001a
Human peripheral lymphocytes (DU)	Sister chromatid exchange	Retained metal fragment	–	McDiarmid et al. 2000, 2004b, 2006
Human peripheral lymphocytes (DU)	HPRT mutation frequency	Retained metal fragment	±	McDiarmid et al. 2004a, 2006, 2007
Human peripheral lymphocytes (DU)	HPRT mutation frequency	Retained metal fragment	–	McDiarmid et al. 2009, 2011a
Human peripheral lymphocytes (DU)	Micronuclei frequency	Retained metal fragment	–	Bakhmutsky et al. 2011
Human peripheral lymphocytes (DU)	PIG-A mutant frequency	Retained metal fragment	±	McDiarmid et al. 2011a
Mouse (BALB/c) (EU)	Sperm DNA damage	Intraperitoneal	+	Hu and Zhu 1990
Rat epithelial nasal cells (DU)	DNA damage	Inhalation	–	Monleau et al. 2006a
Rat broncho-alveolar lavage (BAL) cells (DU)	DNA damage	Inhalation	+	Monleau et al. 2006a
Rat kidney cells (DU)	DNA damage[a]	Inhalation	–	Monleau et al. 2006a

Table 3-5. Genotoxicity of Uranium *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference
Rat kidney cells (DU)	DNA damage[b]	Inhalation	+	Monleau et al. 2006a
Rat bone marrow (DU)	Micronuclei	Oral	+	Hao et al. 2009
Rat sperm cells (DU)	DNA damage	Oral	+	Hao et al. 2009
Mouse bone marrow cells[c] (DU)	Point mutations	Oral	+	Miller et al. 2010
Mouse bone marrow cells[c] (EU)	Point mutations	Oral	+	Miller et al. 2010
Mouse bone marrow cells[c]	Point mutations	Implanted DU pellets	+	Miller et al. 2010

[a]Single exposure.
[b]Repeated exposures.
[c]From offspring of exposed males.

+ = positive result; − = negative result; ± = weak or inconclusive result; DU = depleted uranium; EU = enriched uranium; PIG-A = phosphatidylinositol glycan class-A

With few exceptions, studies of genotoxicity of uranium in eukaryotic cells *in vitro* have yielded positive results (Table 3-6). For example, incubation of Chinese hamster ovary (CHO) cells with uranyl nitrate hexahydrate resulted in significant dose-dependent increases in micronuclei, SCEs, and chromosomal aberrations (Lin et al. 1993). Incubation of human osteosarcoma (HOS) cells with depleted uranium for 24 hours resulted in cell transformation into a tumorigenic phenotype and in significant increases in micronuclei, SCEs, and chromosomal aberrations in the form of dicentrics (Miller et al. 2002b). The increase in dicentrics suggested that the radiological component may play a role in depleted uranium's ability to induce both DNA damage and neoplastic transformation. To further study the role of the radiological component in the genotoxicity of depleted uranium, the same group of investigators incubated HOS cells with one of three uranyl nitrate compounds (^{238}U-uranyl nitrate, specific activity 0.33 μCi/g; depleted uranyl nitrate, specific activity 0.44 μCi/g; ^{235}U-uranyl nitrate, specific activity 2.2 μCi/g) at the same concentration (50 μM) but varying in specific activity (Miller et al. 2002c). The results showed a statistically significant difference in transformation frequency between the three uranyl nitrates that was specific activity-dependent, indicating that radiation can play a role in the genotoxicity of depleted uranium. A subsequent report from these investigators showed that depleted uranium induced *de novo* genomic instability in HOS progeny cells, including delayed micronuclei expression and increased micronuclei frequency (Miller et al. 2003). Delayed reproductive death was evident for many generations. A similar effect was induced by nickel or gamma radiation. Depleted uranium stimulated delayed production of micronuclei up to 26 days after exposure, longer than the 12 days it took the cells to return to normal after exposure to nickel or gamma radiation. Miller et al. (2003) noted that the increase in micronuclei frequency is associated with cell lethality. Although the precise mechanism by which depleted uranium induced genomic instability is unknown, the investigators noted that it might be similar to that for gamma radiation. An additional study by Miller et al. (2002a), demonstrated that depleted uranium (15 nM), in the presence of hydrogen peroxide (2, 4, 6, 8, or 10 mM), can induce the formation of oxidative DNA damage in the absence of significant radioactive decay. The levels of hydrogen peroxide were 100 times higher than physiological levels; thus, the *in vivo* relevance of this finding is not known. A more recent study by Darolles et al. (2010) found differences between the genotoxic mechanisms of depleted and 12% enriched uranium, which is 20 times more radioactive. Significant increases in micronuclei formation were found in mouse embryo fibroblast cells exposed to depleted uranium or enriched uranium; at a given uranium concentration, there were no differences in the number of micronuclei formed after exposure to depleted uranium as compared to enriched uranium. However, the origins of the micronuclei differed between depleted uranium and enriched uranium. Following exposure to depleted uranium, the increase in micronuclei induced by depleted uranium was due to chromosome loss. In contrast, micronuclei formation following exposure to enriched uranium was

Table 3-6. Genotoxicity of Uranium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Eukaryotic cells:				
Human osteosarcoma (HOS) cells (DU)	Micronucleus test	ND	+	Miller et al. 2002b, 2002c, 2003
HOS cell line (DU)	Cell transformation	ND	+	Miller et al. 1998b, 2002b, 2002c
HOS cell line (DU)	Sister chromatid exchange	ND	+	Miller et al. 2002b
HOS cell line (DU)	DNA damage	ND	+	Miller et al. 2002b
Human bronchial fibroblasts (particulate DU)	Chromosomal aberrations	ND	+	Wise et al. 2007
Human bronchial fibroblasts (soluble DU)	Chromosomal aberrations	ND	–	Wise et al. 2007
Human bronchial epithelial cells (particulate DU)	Chromosomal aberrations	ND	+	LaCerte et al. 2010
Mouse embryo fibroblast cell line (DU)	Micronucleus test	ND	+	Darolles et al. 2010
CHO cells	Sister chromatid exchange	ND	+	Lin et al. 1993
CHO cells	Chromosomal aberrations	ND	+	Lin et al. 1993
CHO cells	Micronuclei	ND	+	Lin et al. 1993
CHO EM9 cell line (DU)	Mutation at *hprt* locus	ND	±	Stearns et al. 2005; Coryell and Stearns 2006
CHO EM9 cell line (DU)	DNA damage; DNA adducts	ND	+	Stearns et al. 2005
Rat kidney proximal cells (DU)	DNA damage	ND	+	Thiébault et al. 2007
Rat kidney proximal cells (DU)	Micronuclei	ND	–	Thiébault et al. 2007

Table 3-6. Genotoxicity of Uranium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
pBluescript SK^{+} plasmid from *E. coli* TOP10F' (DU)[a]	DNA damage	ND	+	Yazzie et al. 2003
Salmonella typhimurium TA98 (DU)	Reverse mutation[b]	ND	+	Miller et al. 1998a
Salmonella TA7001-7006 (DU)	Reverse mutation[b]	ND	+	Miller et al. 1998a
Salmonella TA98 (DU)	Reverse mutation[c]	ND	–	Miller et al. 1998a
Salmonella TA7001-7006 (DU)	Reverse mutation[c]	ND	–	Miller et al. 1998a

[a]Incubated with ascorbate.
[b]Urine from rats implanted DU was tested.
[c]Serum from rats implanted DU was tested.

+ = positive result; ± = weakly positive; CHO = Chinese hamster ovary; DU = depleted uranium; ND = no data

primarily due to chromosome breakage. Thus, depleted uranium primarily acted as an aneugenic agent and enriched uranium as a clastogenic agent.

Studies conducted with depleted uranium trioxide partially dissolved in acetone and depleted uranyl acetate fully dissolved in water showed that while both forms were cytotoxic to human bronchial cells *in vitro*, only the partially dissolved depleted uranium trioxide induced chromosome aberrations above background levels (LaCerte et al. 2010; Wise et al. 2007). Wise et al. (2007) speculated that the different results may be related to different uptake mechanisms by the cell. Particulate depleted uranium would be able to enter the cell by phagocytosis, whereas soluble uranium would not. Wise et al. (2007) suggested that if depleted uranium were to be carcinogenic *in vivo*, it would require a high dose or involve a non-genotoxic mechanism.

In addition to causing DNA strand breaks in CHO cells, depleted uranium also produced uranium-DNA adducts. Incubation of CHO cells with depleted uranyl acetate showed the presence of DNA adducts on the order of a few uranium atoms per thousand nucleotides (Stearns et al. 2005). The formation of adducts was concentration- and time-dependent. Characterization of the uranium-induced mutation in CHO cells showed the mutation spectrum to be different from the spectra generated spontaneously or by exposure to hydrogen peroxide or alpha and beta particles (Coryell and Stearns 2006). This suggested that depleted uranyl acetate had distinct effects on cells that result in a mutagenic response. A study that assessed DNA damage in rat kidney (NRK-52^{E}) proximal cells using several methods reported DNA damage and apoptosis occurring in a concentration-dependent manner (Thiébault et al. 2007). Apoptosis cell death was caspase-dependent and activated via the intrinsic pathway of the cells.

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 levels of uranium in the urine. In contrast to urine, tests conducted with rats' serum showed no significant increase in mutations, which was consistent with the low levels of uranium in blood. In support of the view that uranium in the urine and no other factor was responsible for the urine mutagenicity was the fact that the urine from controls, both non-surgical and implanted with an inert tantalum pellet, did not show an increase in mutagenic activity.

3.4 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 1994a, 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 2–4% for 3-month-old children and 0.2–2% 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). There are limited data on the dermal absorption of uranium. In hairless rats, dermal exposure to uranyl nitrate resulted in 0.4% of the dose being absorbed (Petitot et al. 2007a); damage to the skin resulted in higher absorption efficiencies. 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% is in the liver, 8% is in the kidneys, and 10% is 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 postexposure, of 0.08 μg U/g creatinine, with the highest rates around 30 μg/g (McDiarmid et al. 1999b).

3.4.1 Absorption

3.4.1.1 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 >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). The dissolution parameters estimated in an *in vitro* study of uranium oxide at a fuel factory differed from the ICRP default values (Dias da Cunha et al. 2011). The rapid dissolution rat was 0.47/day and the slow dissolution rate was 0.0019/day.

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). The authors' estimated daily mean absorption of inhaled uranium by mill workers was 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 three retired uranium mill workers (4–14 years since last employment as uranium ore crushermen), and three 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 were used to estimate the absorption of uranium by workers accidentally exposed to uranium hexafluoride (USNRC 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). One month following a single intratracheal instillation, the percentage of the dose transferred to the blood from the lungs was 73.7–74.8% for uranium peroxide (7.6 or 195 µg administered) and 38.8–43.9% for uranium tetrafluoride (32 or 301 µg administered); the percent absorbed was not influenced by the instillation concentration (Houpert et al. 1999).

In addition to the uptake of uranium from the lungs, there is some evidence from a study of rats exposed via nose-only exposure to 190 mg/m^3 depleted uranium dioxide 30 minutes/day, 4 days/week for 30 weeks (Houpert et al. 2007c) that uranium may be taken up by the olfactory epithelial pathway and travel along the olfactory neuron to the olfactory bulb.

3.4.1.2 Oral Exposure

Experimental studies in humans consistently show that absorption of uranium by the oral route is <5%. Reported fractional absorptions include a range of 0.005–0.05 (0.5–5%) in a group of 4 males ingesting 10.8 mg uranium in a soft drink (Hursh et al. 1969), 0.001–0.06 (median of 0.009) in 50 males and females exposed to uranium in the diet and drinking water (Limson Zamora et al. 2002, 2003), 0.001–0.005 in 4 subjects ingesting a single dose of 100 mg uranium as depleted uranyl nitrate dissolved in a grapefruit drink (Karpas et al. 1998), <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). Measuring uranium levels in bone ash, Chen et al. (2011) estimated fractional absorption values in several

age groups. The estimated fractional absorption values were 0.030±0.022, 0.030±0.023, and 0.021±0.015 for children aged 7–12 years, children aged 12–18 years, and adults aged 18–25 years. Similar results were obtained in dietary balance studies (Leggett and Harrison 1995; Spencer et al. 1990; Wrenn et al. 1989). A study comparing uranium absorption between subjects primarily exposed to uranium in the diet and subjects exposed to elevated levels of uranium in the drinking water (Limson Zamora et al. 2002, 2003) did not find significant differences in fractional absorption between the two subroutes. This study also found no significant differences in uranium fractional absorption related to gender or age (subjects <25 years compared to those >25 years). 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). A rapid absorption rate (5–15 hours) was estimated in four individuals ingesting a single dose of depleted uranyl nitrate (Karpas et al. 1998).

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, 2 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 Stather 1981; Houpert et al. 2001; Larsen et al. 1984; La Touche et al. 1987; Maynard et al. 1953; Sullivan 1980a), although other studies have reported lower absorption efficiencies. Frelon et al. (2005) estimated that 0.43% of the depleted uranyl nitrate in drinking water was absorbed by rats. 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).

Studies in rats suggest that the primary pathway for gastrointestinal absorption of soluble uranium as depleted uranyl nitrate is through the small intestinal epithelium (Dublineau et al. 2005, 2006) via the transcellular pathway (Dublineau et al. 2005). Uranium was not absorbed from the buccal cavity, stomach, or large intestine (Dublineau et al. 2005). *Ex vivo* experiments provide evidence that uranium is equally absorbed in all regions of the small intestine (Dublineau et al. 2005).

3.4.1.3 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).

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.

A series of *in vitro* and *in vivo* studies conducted by Petitot et al. (2004, 2007a, 2007b) demonstrated that uranyl nitrate is absorbed through the skin. *In vitro*, the first transfer of uranium across hairless rat skin and pig ear skin occurred 3 or 4 hours, respectively, after application of uranyl nitrate (Petitot et al. 2004). However, uranium was transferred across excoriated skin (stratum corneum removed to simulate a wound) in 30 minutes for both rat and pig skin. Application of depleted uranium to the skin of hairless rats *in vivo* resulted in significant increases in uranium levels in muscle at the contamination site 6 hours after application to intact skin and within 30 minutes after application on excoriated skin (Petitot et al. 2007a). Twenty-four hours after application, 0.4% of the dose was absorbed through intact skin (Petitot et al. 2007a). A higher percentage of uranium was absorbed through wounded skin; 38% absorbed through excoriated skin and 2–4% through skin damaged from application of a mild acid solution. In

contrast, severely damaged skin from exposure to a strong acid or base solution, resulted in lower absorption efficiencies than intact skin.

3.4.2 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 body burden is considered to be approximately 90 µg. It is estimated that about 66% of this total is in bone, 16% is in the liver, 8% is in the kidneys, and 10% is 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.

3.4.2.1 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. In another comprehensive autopsy study of a worker at a facility involved in the processing and handling of radioactive material, the highest levels of uranium in soft tissues was found in the respiratory tract, particularly the tracheobronchial lymph nodes (Russell and Kathren 2004). The relative amounts of

uranium in the body were lung > skeleton > spleen > liver > kidney. Relatively high levels of uranium were also found in the urinary bladder, blood, and thyroid. A study of uranium process workers and nearby residents chronically exposed to depleted uranium aerosols detected depleted uranium levels in the urine in 2 of the 18 subjects 20 years after exposure (Parrish et al. 2008). Although the investigators suggest that this finding indicates long-term storage and distribution of depleted uranium, the small number of positive findings and the lack of monitoring data on other potential sources of depleted uranium limit the interpretation of the results.

Urinary excretion data were used in a kinetic model to estimate the maximum uranium kidney concentrations of workers accidentally exposed to uranium hexafluoride (USNRC 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 (USNRC 1990).

In animals, uranium that has been absorbed from the lungs leaves the blood very quickly for distribution to body tissues. Following a single intratracheal instillation, uranium was removed from the lung with retention half-times of 0.6–1.3 (63.6–71.6% absorbed) and 30–35 days (36.4–29.4% absorbed) following instillation of 32 or 301 µg uranium tetrafluoride, and 0.5–1.2 (96.6–90.3% absorbed) and 27–38 days (3.4–9.7% absorbed) following instillation of 7.6 or 195 µg uranium peroxide (Houpert et al. 1999). One month after instillation of either uranium compound, 11.3–20.4% of the uranium dose remained in the carcass, 1.5–4.4% was found in the kidney, and 75.9–84.3% was excreted in the urine. The amount of uranium found in the bones of dogs and rats exposed to uranium for 1 year was related to the solubility of the uranium solubility (Stokinger et al. 1953). The concentrations of uranium in bone were 2.0 and 2.7 µg/g in rats exposed to uranyl nitrate (0.25 mg U/m^3) and uranyl fluoride (0.2 mg U/m^3), respectively; however, exposure to a similar concentration of uranium tetrachloride (0.2 mg U/m^3) resulted in a 10-fold reduction in uranium bone levels (0.2 µg/g). Uranium has also been shown to accumulate in the tracheobronchial lymph nodes, lungs, bones, and kidneys of rats, dogs, and monkeys exposed to uranium dioxide at 5.1 mg U/m^3 for 1–5 years (Leach et al. 1970, 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 et al. 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. 1982a) 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 rad/week (0.018 and 0.033 Gy/week) to lungs and 55 and 64 rad/week (0.55 and 0.65 Gy/week) to lymph nodes, while the total radiation dose for the 5 years approached 500 and 900 rad (5 and 9 Gy) to lungs and 10,000 rad (10 Gy) to lymph nodes. 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). Uranium has been shown to increase in the brain following intermediate-duration inhalation exposure to depleted uranium dioxide; however, the levels rapidly decrease following exposure termination and returned to control levels within 3–8 days (Monleau et al. 2005). Uranium is unequally distributed in the brain, with the highest levels found in the olfactory bulbs, followed by the hippocampus, cortex, and cerebellum.

3.4.2.2 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 to 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 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).

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 mean uranium concentration in wet bone was reported to be 0.33 µg 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% 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 3.4.5). 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 accumulations were 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 et al. 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 et al. 1951). Average uranium accumulations in the kidneys and bone of male mice exposed to uranyl fluoride orally at 452 mg U/kg/day for 28 weeks were 33 µg/pair of kidneys and 145 µg/g bone at 20 weeks (Tannenbaum et al. 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 et al. 1951).

Paquet et al. (2006) examined the distribution of depleted uranium in rats following chronic ingestion of 2.0–2.9 mg U/kg/day as depleted uranyl nitrate in mineral water. In addition to the elevated levels of uranium found in the kidney and bones, uranium accumulated in the teeth and brain. Uranium concentrations in teeth were higher than in the skeleton, suggesting that uranium was deposited on the enamel. Accumulation of uranium in the whole body and individual tissues followed a nonmonotonous pattern that was not predictable by biokinetic models. In the whole body, peak levels were found after 3, 10, and 19 months of exposure. Total uranium levels in the whole body were 51.0, 182, 42.2, 134, 3.8, and 200 ng/g tissue after 1, 3, 6, 10, 12, and 19 months of exposure, respectively. Different patterns of uranium accumulation were found in the lumbar vertebrae and femur (diaphysis and epiphysis regions). In the vertebrae, uranium levels did not significantly change until 570 days of exposure; in contrast, uranium levels in the femur peaked at day 95, decreased at day 186, and increased at days 312 and 570. In the kidneys, uranium levels decreased between months 1 and 12 (220 ng/g tissue to 72.4 ng/g) and then increased again (311 ng/g) at 19 months. The investigators noted that the results could not be adequately explained and that further studies should be conducted. Elevated levels of uranium in the brain were also observed in rats exposed to 3.7 mg U/kg/day as 4.92% enriched uranyl nitrate in mineral water for 90 days (Lestaevel et al. 2005b). The levels of uranium in the brain increased from 75.4 to 86.1 ng; the levels of uranium in the kidneys were also significantly increased from 101.9 to 579.0 ng.

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 et al. 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 et al. 1951).

Arruda-Neto et al. (2004a) examined the accumulation of uranium in bones as a function of uranium dose in young rats exposed to uranyl nitrate in the diet at doses of 0.1–26 mg U/kg/day for 60 days and found a biphasic relationship. The inflexion point was at approximately 6 mg/kg/day and accumulation of uranium in the bone increased linearly at doses higher than 6 mg/kg/day. Another study by this group (Arruda-Neto et al. 2004b) found that uranium was equally distributed in the bone and bone marrow in dogs following a long-term exposure to uranyl nitrate in the diet.

Oral exposure to uranyl nitrate in mineral water for 9 months resulted in significant increases in uranium concentration in the hippocampus and cortex; a 1.5-month exposure resulted in nonsignificant increases in uranium in these brain areas (Bensoussan et al. 2009). Bellés et al. (2005) also reported significant increases in brain uranium levels, as compared to controls, following a 3-month exposure to uranyl acetate; however, there was no statistical relationship between dose and brain uranium levels.

The uranium blood:tissue transfer coefficients were estimated in Wistar rats exposed to 0.5–26 mg U/kg/day as uranyl nitrate in the diet for 60 days (Arruda-Neto et al. 2001). The highest transfer coefficients were found in the kidneys and liver. A plot of the transfer coefficients for skin, brain, intestine, heart, liver, and kidneys exhibited concave shapes with the point of deflection occurring at the 5 mg U/kg/day dose level in all tissues except the intestines. The investigators suggested that this may indicate that similar mechanisms are involved in the uptake of uranium by different tissues. Additionally, the slope of the uranium tissue concentration versus dietary concentration increased gradually at the lower doses (<5 mg U/kg/day) and steeply at doses of 5–26 mg U/kg/day. This could be due to an enhanced absorption at uranium doses >20 mg U/kg/day. However, increases in occult blood levels in the urine were also observed at the higher doses, suggesting that the sharp increase in tissue uranium levels may be due to renal damage resulting in an increased concentration of uranium in blood and consequently in organs and tissues.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of uranium after dermal exposure in humans. In hairless rats dermally exposed to depleted uranium in a nitric acid solution, increased levels of uranium were detected in the kidneys and bone 6 hours after application to intact skin; the highest concentrations were found in the kidney (Petitot et al. 2007a). Application to wounded skin (via mechanical abrasion or

exposure to weak acids) resulted in significant increases in uranium levels in the kidneys and bone within 30 minutes of exposure.

3.4.2.4 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 <0.5% after 100 hours although inter-subject variation was high (AEC 1948, 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 postinjection, 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 following implantation of depleted uranium pellets into the gastrocnemius muscle has been investigated in rats (Pellmar et al. 1999a; Zhu et al. 2009a). Within 1 day of implantation, 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, especially the spleen, liver, and lung; the levels were always highest in the kidney and bone. The amount of uranium in the kidney and bone was significantly correlated with the uranium dose. Tissue uranium levels peaked 90 days after implantation and gradually decreased; however, the levels were still elevated 360 days postimplantation (Zhu et al. 2009a).

3.4.3 Metabolism

Uranium is usually found in compounds that 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).

3.4.4 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 <1% of the excretion (ICRP 1995).

3.4.4.1 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 >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 >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).

Lu 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 postaccident day 60 and returning to normal at about postaccident 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 postaccident day 1 was reported as 804.2 µg or approximately 2.6 µg/g of kidney.

Depleted uranium was detected in the urine of uranium process workers and nearby residents 20 years after chronic exposure to depleted uranium aerosols (Parrish et al. 2008). 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, 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 were 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. 1982a). 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 gastrointestinal tract (higher fecal excretion with higher AMAD) by mucocilliary action. Urinary excretion was 25–50% of initial lung burden on day 1 and 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 et al. 1986). In one study with rats, most of the inhaled uranium, as uranium dioxide, was excreted in the urine. In dogs, <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. 1982a), 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 intratracheal 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 et al. 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, 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, 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. 1982a). 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, <1% of the uranium remained in the kidneys after 30 days (Morrow et al. 1982a).

In rats receiving an intratracheal instillation of uranium tetrafluoride or uranium peroxide, urinary excretion of uranium steadily increased during the first 8 days after instillation and then remained constant until the end of the study (postexposure day 30) (Houpert et al. 1999). Two dose levels were administered for each compound, and despite signs of renal toxicity at the high dose level, there were no difference in the K/K+U ratio (K is the percent of uranium retained in the kidneys and U is the percent excreted in urine) between the groups.

3.4.4.2 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 three villages near uranium mining and refining facilities and a control village in Japan were <0.02–0.24 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% is excreted within 7 days (Sullivan et al. 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 (La Touche et al. 1987; Sullivan 1980a; Sullivan et al. 1986).

Data from parenteral studies provide further indication that uranium retention in animal kidneys is described by a two-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 (DOE 1986b).

A nonmonotonous pattern of uranium excretion was observed in rats chronically exposed to 2.0–2.9 mg U/kg/day as depleted uranyl nitrate in drinking water (Paquet et al. 2006). The highest excretion levels were observed after 6 months of exposure (200 ng U/mL), after which time the levels steadily declined. At approximately 13 months of exposure, the levels remained constant at 30 ng U/mL for the last 6 months of the study.

3.4.4.3 Dermal Exposure

No studies were located describing the excretion of uranium following dermal exposure in humans. Application of depleted uranium or uranium in a nitric acid solution resulted in significant increases in the urinary excretion of uranium within 24 hours of exposure in hairless rats (Petitot et al. 2007a, 2007b). Application to intact skin resulted in increases in urinary uranium within 2 hours of exposure; application to wounded skin (via mechanical abrasion or exposure to low concentration of an acid solution) resulted in increases in urinary uranium within 30 minutes of exposure. In contrast, severe damage to the skin resulted in low levels of uranium in the urine, first detected 6 hours after exposure.

3.4.4.4 Other Routes of Exposure

One day after depleted uranium pellets were implanted in the gastrocnemius muscle of rats, increased levels of uranium were measured in the urine (Zhu et al. 2009a). Urinary excretion peaked 90 days after implantation and remained elevated 360 days after implantation.

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

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

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

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

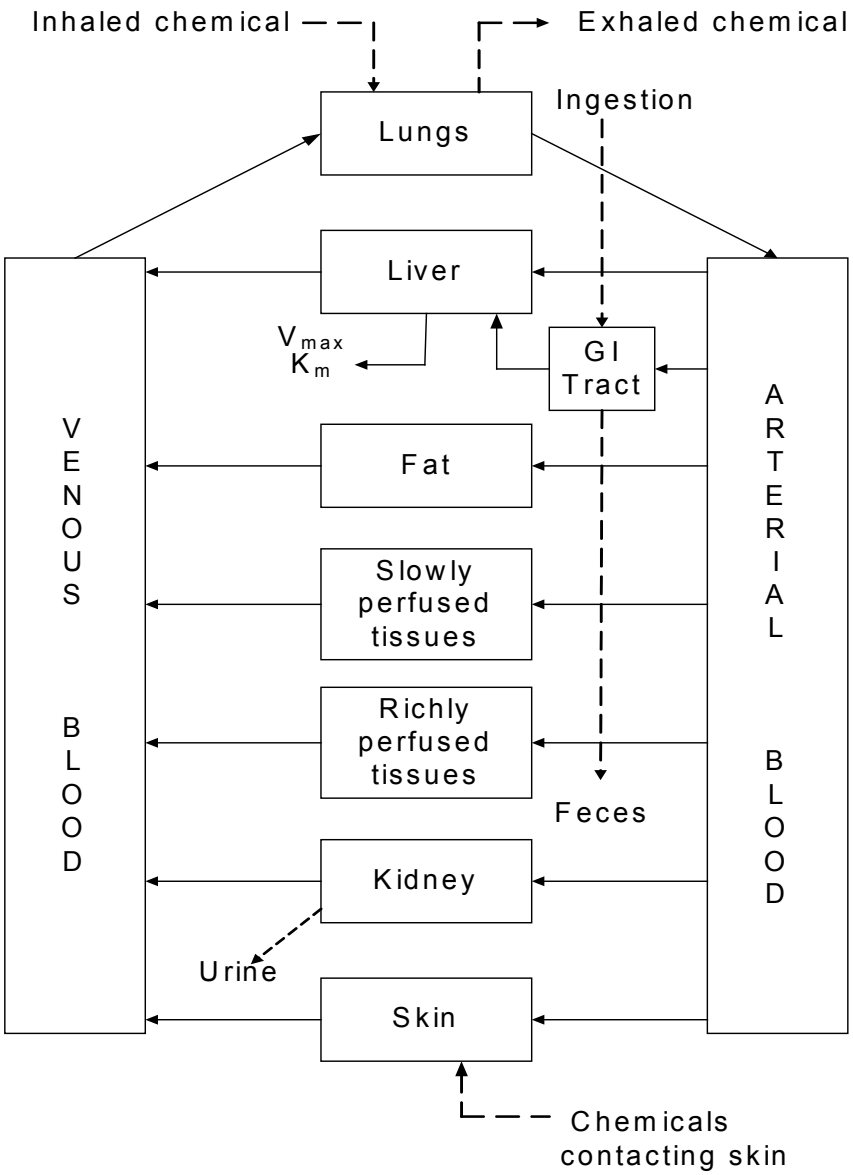
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figures 3-3 through 3-9 show models for radionuclides in general or specifically for uranium.

If PBPK models for uranium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

The ICRP (1994a, 1996) developed a Human Respiratory Tract Model (HRTM) 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. Several more recent enhancements to the oral exposure model

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



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

Source: adapted from Krishnan and Andersen 1994

have been reported. A multicompartmental gastrointestinal tract model was developed to replace what was originally a single parameter model (Human Alimentary Tract Model, HATM; ICRP, 2006a). A hair compartment was developed to support biomonitoring of ingestion intakes (e.g., drinking water exposures, Li et al. 2009a). Drinking water and dietary exposure models and Bayesian approaches have been developed to improve uranium dose assessments made with the ICRP model (Little et al. 2003, 2007). A biokinetics model for embedded uranium has been developed based on studies of uranium kinetics in rats that received implants of depleted uranium pellets (Leggett and Pellmar 2002; Squibb et al. 2005). An adaptation of the ICRP human model for simulating biokinetics of inhaled uranium in rats has been reported (Monleau et al. 2006b) and the rat model was used to evaluate the general assumption of linear kinetics in the ICRP model (i.e., kinetics are independent of the dose history). Several quantitative uncertainty analyses of the ICRP model have been reported (Davesne et al. 2009; Farfan et al. 2003; Puncher et al. 2008). The ICRP model performance has been evaluated against data on urinary excretion of uranium and data on uranium levels in tissues obtained from autopsy studies (Li et al. 2005, 2006, 2009a; Russell and Kathren 2004). Several recent applications of the ICRP model to exposure and risk assessment have been reported. The model has been applied to simulate uranium body burdens and radiation doses associated with exposure scenarios of releases of depleted uranium in vehicles impacted by depleted uranium munitions (Guilmette et al. 2009). The embedded uranium model developed by Leggett and Pellmar (2002) has been extended to humans and has been applied to predicting kidney uranium burdens in military veterans who received embedded fragment wounds resulting from vehicles impacted with depleted uranium munitions (Squibb et al. 2005). A wound biokinetic model developed by NCRP (2008) has been coupled with the ICRP model to calculate predicted urinary excretion patterns and uranium kidney retention for different categories of uranium exposure (NCRP 2008). An extension of the ICRP model that includes simulation of the transfer of uranium to hair has been used to estimate uranium dose coefficients for ingestion of uranium in drinking water (Li et al. 2009a). The model has been used to predict radiation doses associated with exposures to uranium in drinking water and uranium body burdens associated with ingestion and inhalation exposures (Chen et al. 2004; Li et al. 2009b).

The NCRP has also developed a respiratory tract and biokinetics model for inhaled radionuclides (NCRP 1997). Four other compartmental models (Fisher et al. 1991; Sontag 1986; Valdés 2009; Wrenn et al. 1994) are also described below.

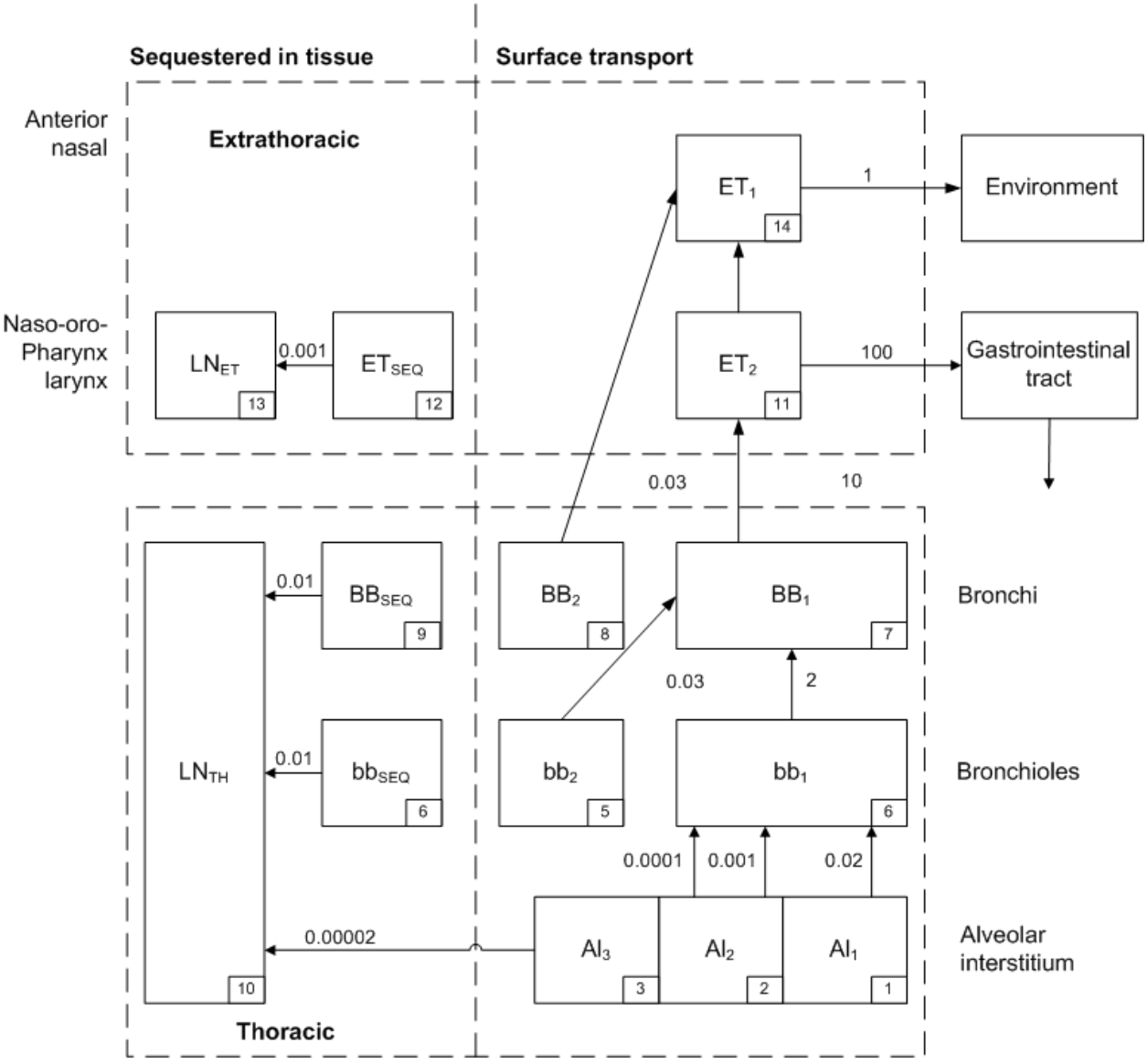
Human Respiratory Tract Model for Radiological Protection (ICRP 1994a, 1996)

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 that 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 3-4). The model was developed with five compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed 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 3-7 provides reference respiratory values for the general Caucasian population under several levels of activity.

Figure 3-4. Respiratory Tract Compartments in Which Particles May be Deposited*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-8.

Source: ICRP 1994a

Table 3-7. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

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

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

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

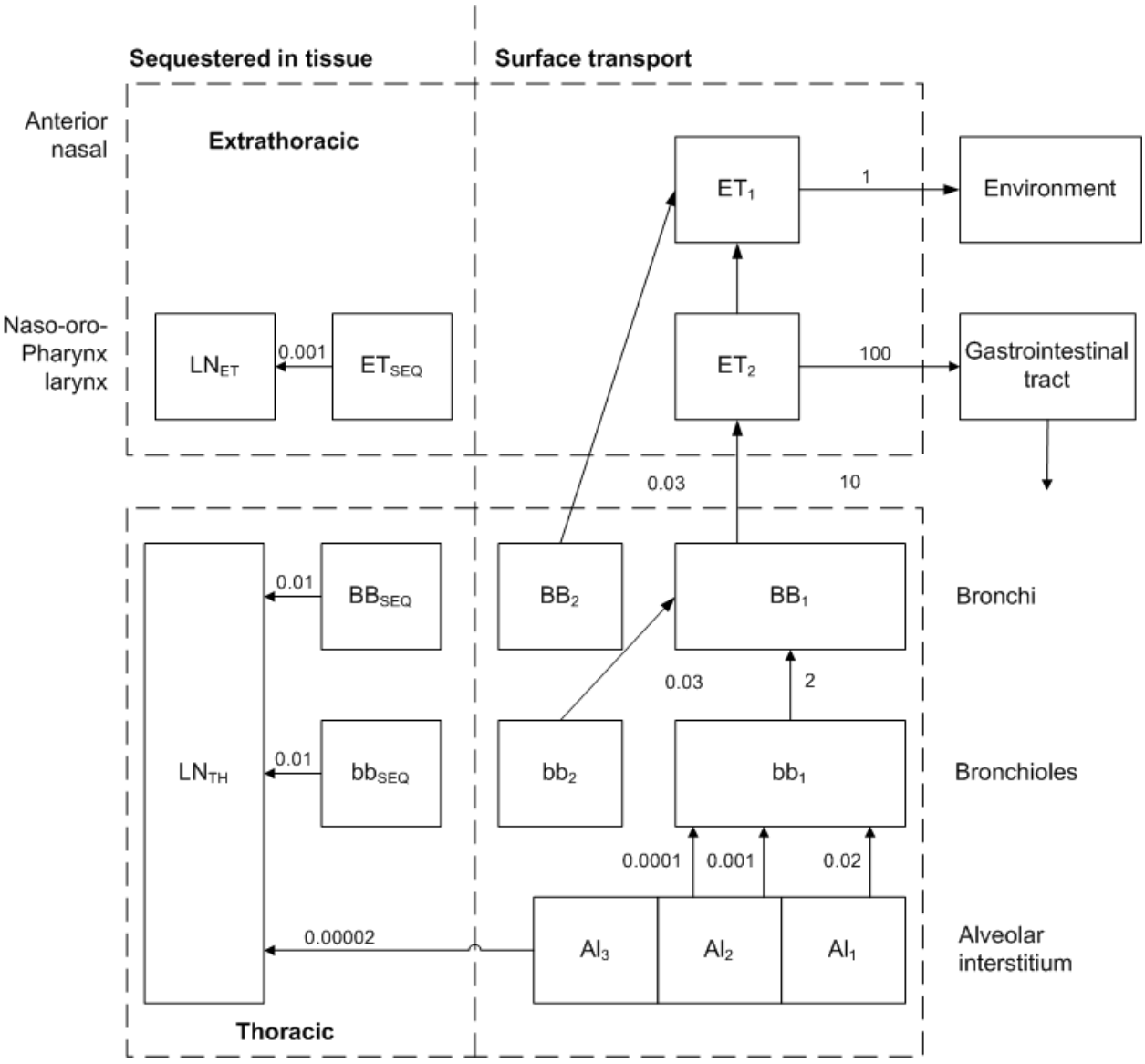
Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. Figure 3-5 presents the compartmental model and is linked to the deposition model (Figure 3-4) and to reference values presented in Table 3-8. Table 3-8 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

Figure 3-5. Environmental Pathways for Potential Human Health Effects from Uranium



See Table 3-8 for rates, half-lives, and fractions by compartment.

Source: ICRP 1994a

Table 3-8. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

Clearance rates for insoluble particles				
Pathway	From	To	Rate (d^{-1})	Half-life[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	$1x10^{-4}$	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	$2x10^{-5}$	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

Table 3-8. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

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

[a]The half-lives are approximate since the reference values are specified for the particle transport rates and are rounded in units of days^{-1}. A half-life is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-life of compartment AI_3 is determined by the sum of the clearance rates.
[b]See paragraph 181, Chapter 5 (ICRP 1994a) for default values used for relating f_s to d_{ae}.
[c]It is assumed that f_s is size-dependent. For modeling purposes, f_s is taken to be:

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

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

where

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

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

Source: ICRP 1994b

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 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 three subcompartments to represent different clearance rates, all of which are slow.

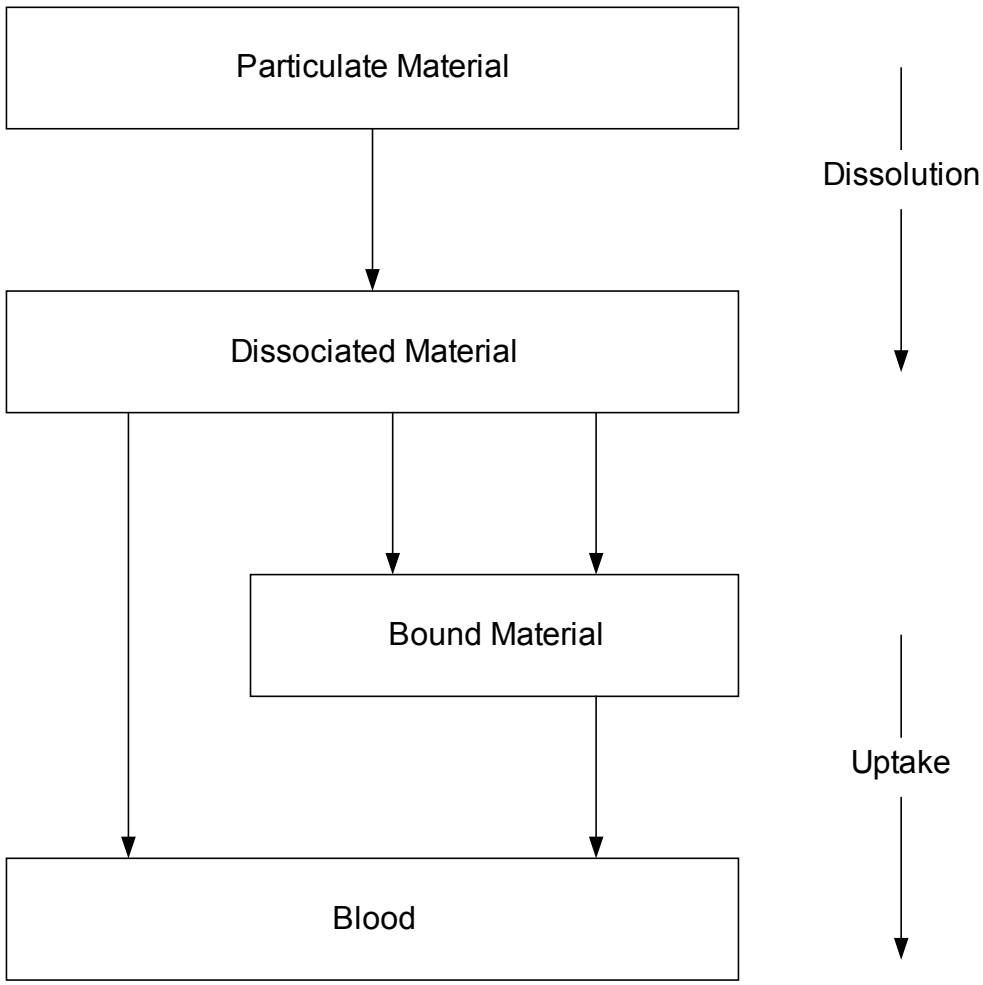
In the alveolar-interstitial region, human lung clearance has been measured. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time and the remaining 70% are given a half-time of several hundred days. Over time, AI particle transport falls and some 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 two-stage process, as shown in Figure 3-6. 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

Figure 3-6. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994a

can behave as Type F), ammonium diuranate, uranium oxtaoxide (which can behave as Type S), and uranium tetrafluoride (which can behave as Type F).

- 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).

Human Alimentary Tract Model for Radiological Protection (ICRP 2006a)

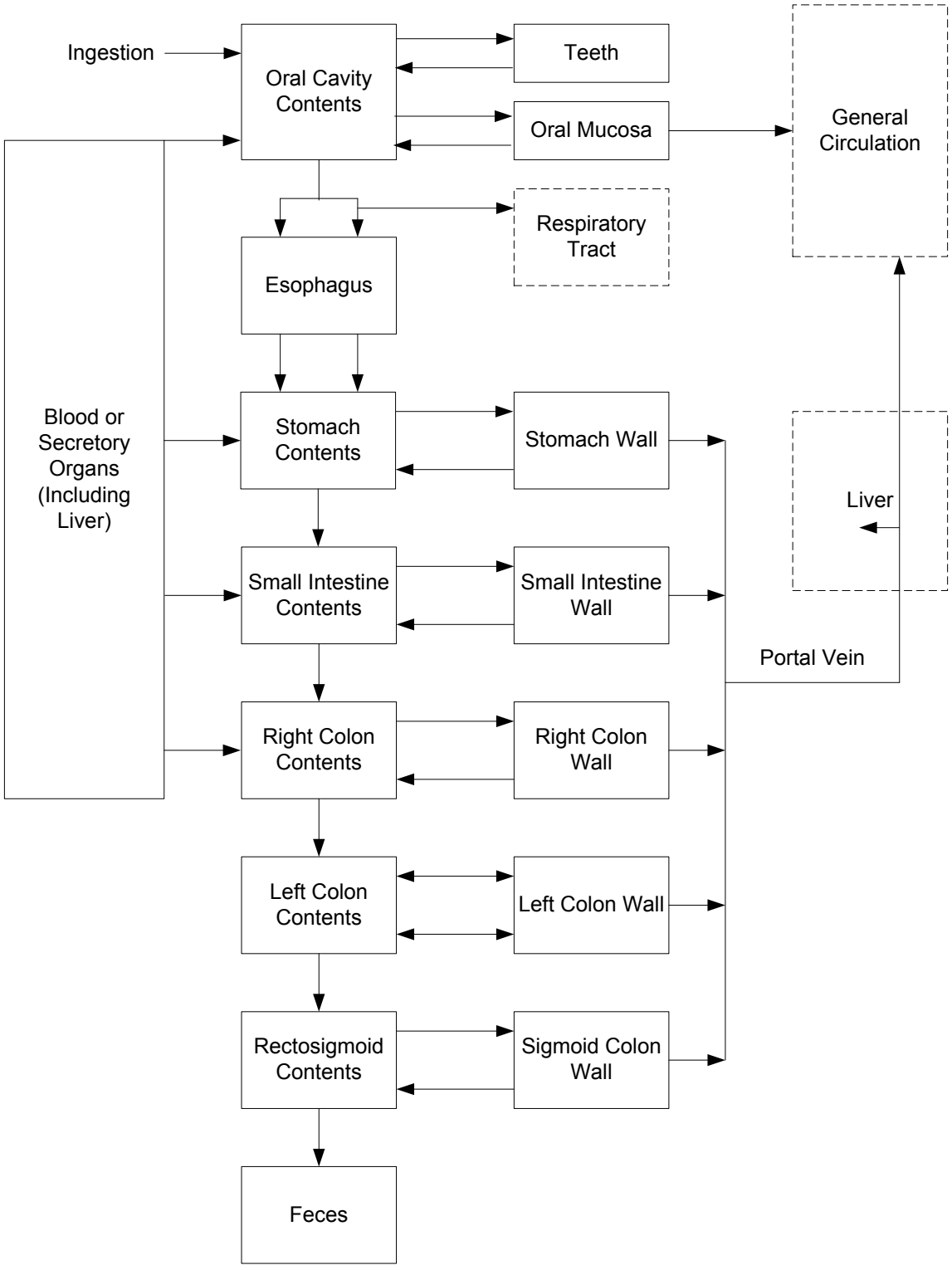
The ICRP HATM is a generic multicompartment gastrointestinal tract model that was developed for applications to radiation risk assessments of radionuclides. The model replaced an earlier gastrointestinal absorption model that consisted of single compartment and single parameter representation of absorption of radionuclides into the central plasma compartment from the small intestine. The structure of the multicompartment model is shown in Figure 3-7. The model simulates the following major processes that can contribute to absorption of radionuclides from the gastrointestinal tract and contact and retention radionuclides in the gastrointestinal tract tissues (i.e., which could contribute to radiation dose to these tissues):

- Entry of a radionuclide into the mouth by ingestion, or into the esophagus after mechanical clearance from the respiratory tract; sequential transfer of the radionuclide through the contents of the oral cavity, esophagus, stomach, small intestine, and segments of the colon, followed by excretion in feces.
- Deposition and retention on or between the teeth and return to the oral cavity.
- Deposition and retention in the oral mucosa or walls of the stomach and intestines.
- Transfer from the oral mucosa or walls of the stomach and intestines back into the luminal contents or into blood (absorption).
- Transfer from various secretary organs or blood into the contents of certain segments of the alimentary tract (secretion).

Biokinetic Model for Uranium (ICRP 1995, 2006a)

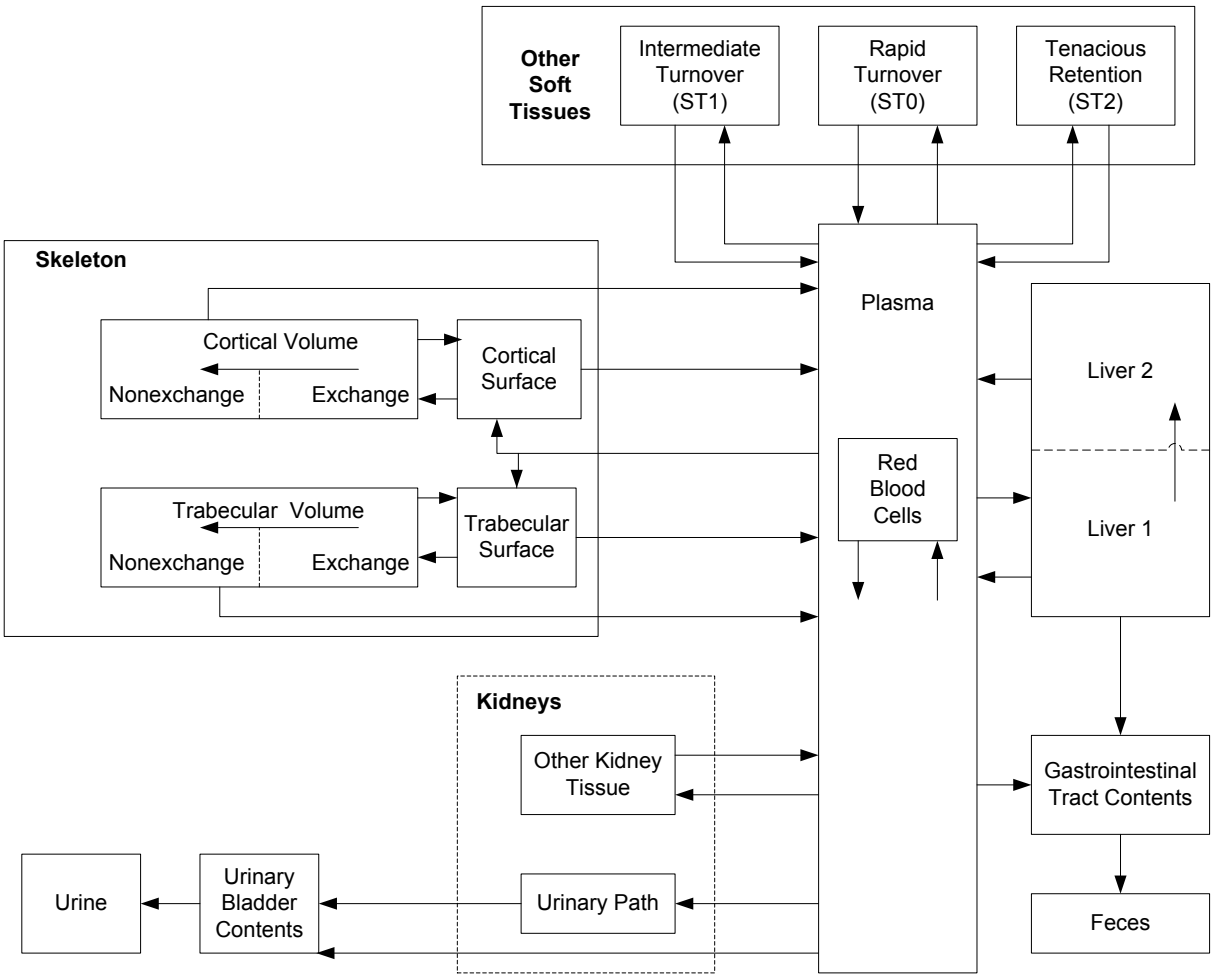
The ICRP biokinetic model for uranium is based on the generic model structure for alkaline earth elements described in *Publication 67* (ICRP 1994b, 1995) linked to a generic multicompartmental alimentary tract model (HATM) described in *Publication 100* (ICRP 2006a). The structure of the model is shown in Figure 3-8. Uranium (as the UO_2^{2+} ion) is similar to calcium (Ca^{2+}) with regard to skeletal kinetics.

Figure 3-7. Structure of the Human Alimentary Tract Model (HATM)



Source: ICRP 2006a

Figure 3-8. Biokinetic Model for Uranium after Uptake to Blood



Source: ICRP 1995

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. 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.

Valdés (2009) Lung Model

A multicompartment model for predicting lung burdens of uranium resulting for exposure to depleted uranium aerosols was proposed by Valdés (2009). Clearance of uranium particles deposited in the lung is assumed to occur by mechanical clearance by the mucociliary escalator and by cellular transport of uranium particles to lymph nodes after phagocytosis by macrophages. The model assumes that phagocytosis is sufficiently rapid that essentially all absorption of uranium can be assumed to occur from macrophages after intracellular dissolution of uranium oxides to uranyl ion in macrophage lysosomes. The macrophage plasma membrane is assumed to be transparent to uranyl ion (i.e., absorption to the systemic circulation is considered to be essentially instantaneous). Therefore, the rate of absorption of uranium into the systemic circulation is determined by the dissolution rate, which is assumed to have fast and slow rate components. This representation of fast and slow dissolution kinetics and essentially instantaneous absorption of dissolved uranium is conceptually similar to the ICRP HRTM (ICRP 1995,

1996). A competing process within macrophages is precipitation of uranyl phosphates within lysosomes. Uranyl phosphate precipitates are assumed to be kinetically inert and are stored permanently in lymph nodes. Uranium absorbed into the systemic circulation is distributed and excreted according to the systemic biokinetics model based on the model developed by Wrenn et al. (1994).

The lung model is implemented as a series of first-order differential equations, the core of which are as follows. The amounts of uranium oxides in lungs (L) and lymph nodes (N) at time, t, following initial deposition in the lung of amount A_0 are given by:

$$L(t) = A_0(0.0142e^{-2.1512t} + 0.3042e^{-0.00201t} + 0.0261e^{-0.2812t} + 0.0107e^{-0.0023t})$$

$$N(t) = A_0[0.0024(e^{-2.15t} - e^{-2.1512t}) + 0.0018(e^{-0.0011t} - e^{-0.0023t}) + 0.0567(e^{-0.00081t} - e^{-0.00201t}) + 0.0044(e^{-0.28t} - e^{-0.2812t})]$$

A similar set of expressions represents the amount of insoluble uranyl phosphates in lungs (P_L) and lymph nodes (P_N) at time, t, following initial deposition in the lung of amount A_0:

$$P_L(t) = A_0(1.460e^{-0.0012t} - 1.419e^{-0.00201t} - 0.0238e^{-2.1512t} - 0.0094e^{-0.2812t} - 0.008e^{-0.0023t})$$

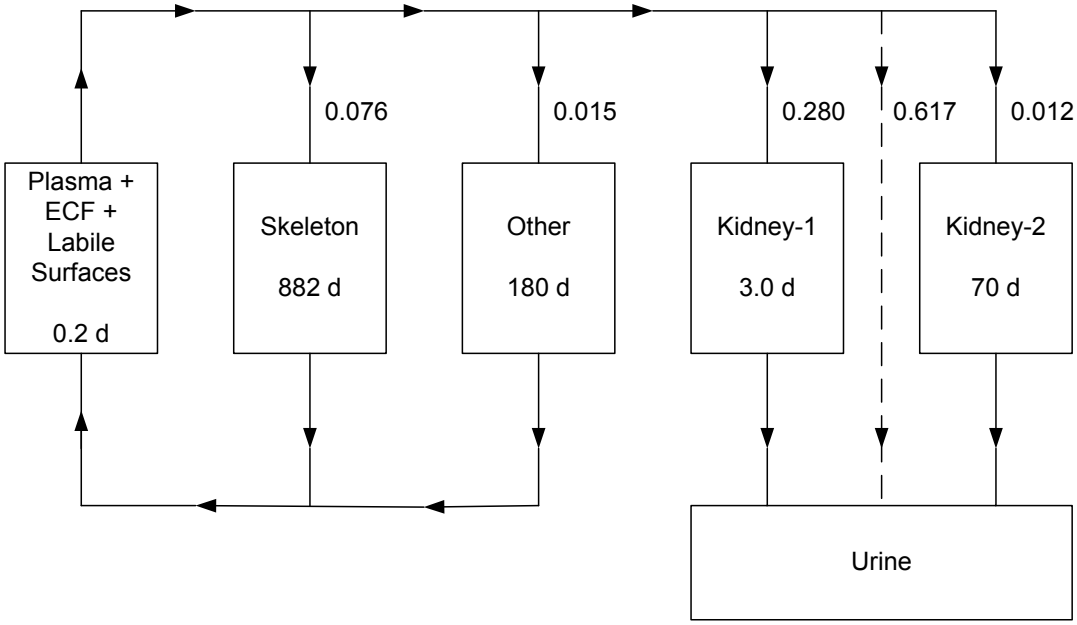
$$P_N(t) = A_0(0.1015 + 2.2164x10^{-6}e^{-2.1512t} + 0.1412e^{-0.00201t} + 6.6816x10^{-6}e^{-0.2812t} + 0.0007e^{-0.0023t} - 0.2434e^{-0.0012t})$$

The Valdés (2009) model has been applied to estimating initial and current body burdens of uranium in military veterans who were exposed to depleted uranium aerosols, based on time history of urinary uranium measurements.

Wrenn et al. (1994) Pharmacokinetic Model

A multicompartment model of distribution and excretion of absorbed uranium was proposed by Wrenn et al. (1994), based on data collected in studies conducted in nonhuman primates and in other animal models and data on tissue levels and urinary excretion of uranium in humans. The model includes a central compartment consisting of plasma and extracellular fluid (ECF), which exchanges uranium with the skeleton, kidney, and a lumped compartment representing all other soft tissues (see Figure 3-9). The skeleton is represented as a single compartment, unlike the ICRP model (ICRP, 1995), which subsequently adopted a multicompartment representation for the skeleton. The kidney includes slow and fast kinetics compartments, both of which contribute to urinary uranium. Uranium is also transferred to urine directly from plasma.

Figure 3-9. Multicompartmental Model for Uranium after Uptake to Blood



Source: Wrenn et al. 1994

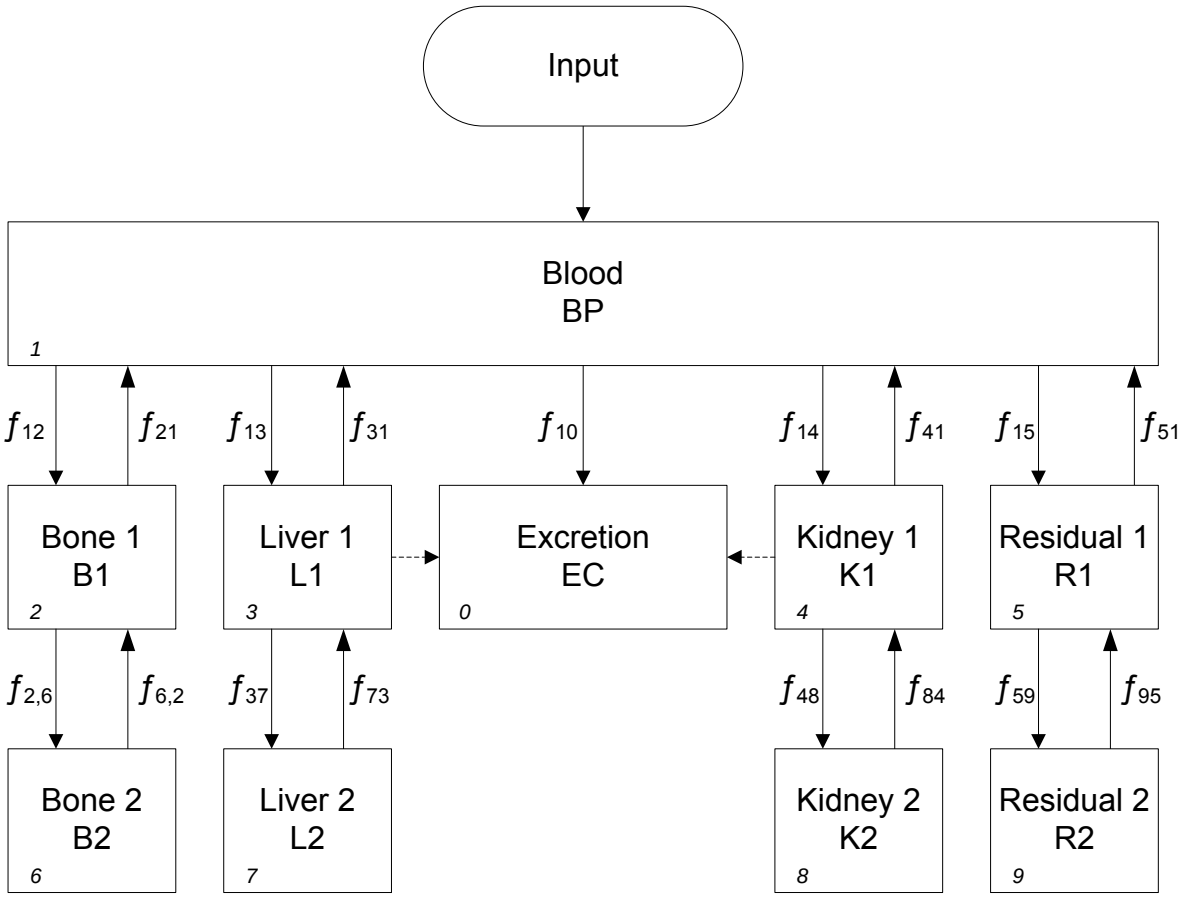
Sontag (1986) Pharmacokinetic Model

An extended multicompartmental model (see Figure 3-10) 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.

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 3-9.

Parallel evaluations produced two 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).

Figure 3-10. Multicompartmental Model



f = transfer coefficient (unitless)

Source: Sontag 1986

Table 3-9. Sensitivity and Calculated Transfer Coefficients (d^{-1})

Transfer from-to	Symbol	Experimental value 1	Experimental value 2	Sensitivity
BP-EC	f_{10}	555	209	0.2
BP-B1	f_{12}	56.3	39.9	5.9
BP-L1	f_{13}	12.7	7.94	3.3
BP-K1	f_{14}	141	2.60	1.5
BP-R1	f_{15}	28.4	26.1	17.5
B1-BP	f_{21}	0.00979	0.0184	1.9
L1-BP	f_{31}	0.187	0.270	5.6
K1-BP	f_{41}	0.0948	0.365	0.5
R1-BP	f_{51}	0.225	0.341	3.4
B1-B2	f_{26}	0.00565	0.00649	2.2
L1-L2	f_{37}	0.00863	0.00940	2.7
K1-K2	f_{48}	0.00114	0.00122	2.2
R1-R2	f_{59}	0.0103	0.00860	6.1
B2-B1	f_{62}	0.00261	4.43×10^{-6}	5.0
L2-L1	f_{73}	0.00284	0.00349	43.7
K2-K1	f_{84}	0.000972	0.00122	4.8
R2-R1	f_{95}	0.000716	0.00138	2.3
Varinz	V	0.00663	0.00465	Not applicable

Source: 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.

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 to 6 days and the clearance half-time in the lung from 0.5 to 0.03 days optimized the fit of the model to the experimental data. The model may be summarized with the following five-term exponential equation:

$$y_u(t) = 1.5e^{-2.77t} + 0.028e^{-0.116t} + 0.0069e^{-0.0347t} + (4.8x10^{-7}e^{-0.000462t}) + 3.2x10^{-6}e^{-0.000139t}$$

where, $y_u(t)$ is fractional daily uranium excretion rate at t days after intake; the excretion constants in the five 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 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 kidney tissue; renal toxicity was not observed in any of the workers (Fisher et al. 1991; USNRC 1990).

Based on this same data base, the USNRC 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), excluding radon, in the area from which the data were collected (USNRC 1986).

3.5 MECHANISMS OF ACTION

3.5.1 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 (EPA 1988d; Harrison and Stather 1981; Hursh et al. 1969; ICRP 1979; Larsen et al. 1984; La Touche et al. 1987; Leggett and Harrison 1995; Maynard et al. 1953; Sullivan 1980a; Wrenn et al. 1985). 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 >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 et al. 1953).

In an *in vitro* study by Vidaud et al. (2005), several uranium binding proteins were identified in human serum including haptoglobin, apolipoprotein A1, serum albumin, α-1-antitrypsin, IgG, α-1-acid

glycoprotein, holotransferrin, hemopexin, apotransferrin, complement C4, complement C3, and ceruloplasmin. Uranium was not shown to bind with retinol binding protein, transthyretin, or tropomyosin. It is not known if these proteins are involved in the distribution of uranium to other tissues.

3.5.2 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; Spoor and Hursh 1973; Spiegl 1949; Stokinger et al. 1953).

The most sensitive target of uranium toxicity to mammals, and perhaps humans, is the kidney. While acute, high-level exposure to uranium compounds can clearly cause nephrotoxicity in humans (Lu and Zhao 1990; Pavlakis et al. 1996), 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 (Checkoway et al. 1988; Dupree et al. 1987; Lundin et al. 1969; NIOSH 1987; 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 1956; Hursh and Spoor 1973; Luessenhop et al. 1958), or after war-related exposures (McDiarmid et al. 2000, 2001a, 2004b, 2006, 2007, 2009). A comparison of autopsy kidney tissue samples revealed no differences between seven uranium workers and six 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 >1 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. 1982a). Excessive urinary excretion of protein, glucose, amino acids, or enzymes, 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. 1982a).

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 pulmonary fibrosis in acute exposures or to hyperplasia, hypertrophy, and transdifferentiation (metaplasia) in chronic exposures (Clayton and Clayton 1981; Cooper et al. 1982; Dungworth 1989; 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 4–8 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.

3.5.3 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; Clayton and Clayton 1981; Cooper et al. 1982; Dungworth 1989; 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 (AEC 1957; Fisher et al. 1991; Kathren and Moore 1986; Lu and Zhao 1990; Luessenhop et al. 1958; Thun et al. 1985; USNRC 1986; Waxweiler et al. 1981a) 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.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997a). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Only one study was located that provided information regarding potential neuroendocrine effects of uranium (Raymond-Whish et al. 2007). In that study, 28-day-old ovariectomized female mice received doses of approximately 0.005, 0.009, 0.09, or 0.9 mg U/kg/day in tap water for 30 days. Ovariectomy was performed to remove the endogenous source of estrogen. A group of mice was also exposed to diethylstilbestrol (DES) as a positive control. Exposure to 0.009 mg U/kg/day significantly increased

uterine weight, but the higher doses were without significant effect. In addition, mice exposed to 0.005 or 0.009 mg U/kg/day had significantly increased presence of cornified vaginal cells relative to controls, which indicated an estrogenic effect of uranium. In a different experimental series, the investigators studied the dependency of the estrogen-like effects of uranium on estrogen receptor (ER) activation. Ovariectomized mice received the same doses for 10 days beginning at 50 days of age. A group of mice also received injections of an anti-estrogenic drug. Doses of 0.005 mg U/kg/day, but not higher doses, significantly increased uterine weight and the effect could be blocked by the anti-estrogenic compound. Also, exposure to 0.009 mg U/kg/day significantly accelerated vaginal opening, which was also blocked by the anti-estrogenic drug. A mechanism by which uranium evoked estrogenic responses was not defined.

No *in vitro* studies were located regarding endocrine disruption of uranium.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to

body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

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 (Lu and Zhao 1990) or intentionally (Pavlakis et al. 1996). No reports are available of studies where toxic responses of young animals to uranium were directly compared to those of adults. Three studies by Maynard et al. (1953) evaluated age-related differences in uranyl nitrate toxicity in rats aged 17 days to 6 months exposed to 2% uranyl nitrate in the diet for 30 days; in rats aged 1, 2, 3, or 6 months exposed to 2% uranyl nitrate in the diet for 24 hours followed by a 30-day observation period; and in rats aged 21 days to 6 months receiving a single intraperitoneal injection of 128 (males) or 200 (females) mg/kg uranyl nitrate hexahydrate. Both studies

found age-related increases in mortality. In the 30-day dietary exposure study, >75% of the 17- and 21-day-old animals died during the study, <10% of the 28-day-old animals died, and >50% of the 2-, 3-, 4-, 5-, and 6-month-old animals died. Insufficient body weight and food intake data were provided; thus, daily doses cannot be calculated. The 1-day dietary study found a similar pattern of mortality. Mortality increased with age; 1% (males) and 3% (females) of the 1-month-old rats died compared to 8% (males) and 16% (females) of the 6-month-old rats. Following a single intraperitoneal dose, the mortality rates were 36, 11, 8, 18, 24, and 19% males and 24, 18, 8, 23.5, 41, 22, and 52% of the females aged 21 days, 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months, respectively. The differences in mortality may be due to age-related toxicokinetic differences, such as changes in absorption efficiency, skeletal development, or kidney development.

Several investigators (as reviewed by Busby et al. 2010; Hindin et al. 2005) have examined the possible association between exposure to depleted uranium and birth defects. Interpretation of these data is limited by the lack of adequate controls, monitoring data to determine whether the subjects were exposed to depleted uranium and at what level, potential exposure to other agents, and other possible confounding factors, such as poor nutrition. Animal studies have examined the developmental toxicity of uranium compounds following oral exposure or intramuscular implantation. Developmental effects (described in greater detail in Section 3.2.2.6) have been observed in rats and mice following oral exposure (gavage or drinking water administration) to soluble uranium compounds; the effects include decreases in viability or embryolethality (Domingo et al. 1989b, 1989c; Paternain et al. 1989), decreases in fetal body weight (Domingo et al. 1989c; Paternain et al. 1989), increases in the number of litters with visceral and skeletal defects (e.g., cleft palate, bipartite sternebrae, reduced ossification) (Domingo et al. 1989c), alterations in performance on neurobehavioral tests (Houpert et al. 2007a; Sánchez et al. 2006), alterations in ovarian folliculogenesis (Arnault et al. 2008; Raymond-Whish et al. 2007), and delayed tooth eruption (Pujadas Bigi and Ubios 2007; Pujadas Bigi et al. 2003). No developmental effects were observed in offspring of rats following implantation of depleted uranium pellets in the gastrocnemius muscle (Arfsten et al. 2009).

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). In contrast, another oral exposure study (Sánchez et al. 2006) found elevated uranium levels in the offspring of rats exposed to uranyl acetate prior to mating and throughout gestation and lactation, suggesting transplacental and/or lactational transfer of uranium. 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 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 1994b) 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.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for uranium from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to uranium are discussed in Section 3.9.1.

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

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or

other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Uranium

The primary biomarker of exposure to uranium is the chemical or radiological detection of total uranium or individual uranium isotopes 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. 1982a; 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. Uranium can also be measured in feces, nails, and hair (Karpas 2001; Karpas et al. 2005a, 2005b; Muikku et al. 2009). Although elevated uranium levels could only be measured in urine and fecal samples within days of acute exposure to uranium, elevated uranium levels could be measured in hair and nail samples weeks or months after the acute exposure (Karpas 2001; Karpas et al. 2005a, 2005b). In humans chronically exposed to elevated uranium levels in drinking water, good correlations were found for daily uranium intake with hair uranium levels and with nail uranium levels (Karpas et al. 2005b). Muikku et al. (2009) noted that in areas of high uranium in drinking water, a portion of the uranium content in hair may be due to external contamination and this proportion needed to be quantified before using hair uranium levels to estimate uranium ingestion. Karpas et al. (2005a) also found that the isotopic ratio of ^{234}U to ^{238}U in hair and toenail samples correlated with that of drinking water (primary route of exposure for the study population) and could be used to identify the source of exposure.

Twenty-four hour urine samples, corrected per gram creatinine concentration, are considered the "gold standard" for assessing uranium body burden. To evaluate the accuracy of spot urine samples for assessing uranium body burden, McDiarmid et al. (1999b) examined 22 non-uranium exposed veterans and 29 veterans exposed to depleted uranium. In both groups, the median and mean urine uranium levels were similar in the creatinine-corrected 24-hour samples and spot samples. When both groups were combined, the 24-hour creatinine-corrected urine uranium levels were highly correlated (R^2=0.97) with the creatinine-corrected spot urine uranium levels. However, lower correlation coefficients were found in the non-exposed group (R^2=0.44) and in exposed veterans with 24-hour urine uranium levels of <0.05 µg U/g creatinine (R^2=0.48). In contrast, the correlation coefficient was 0.99 in the veterans with 24-hour urine uranium levels of ≥0.05 µg/g creatinine. Marco et al. (2008) also found that spot urine samples

normalized to creatinine concentration were representative of 24-hour uranium levels among workers at a nuclear research center.

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.

3.8.2 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 (Lu and Zhao 1990; Pavlakis et al. 1996; Thun et al. 1985; Waxweiler et al. 1981a) and in animal (Leach et al. 1970, 1973, 1984; Morrow et al. 1982a; Stokinger et al. 1953) studies. Increases in the urinary excretion of several biomarkers, including β_2 microglobulin, protein HC, and retinol binding protein, have been observed in populations consuming elevated levels of uranium in drinking water (Kurttio et al. 2002; Limson Zamora et al. 1998, 2009; Mao et al. 1995; Seldén et al. 2009). These biomarkers, although not specific to uranium, could be used to as sensitive biomarkers of renal dysfunction. In rats receiving a single intramuscular dose of depleted uranium nitrate, there was a high correlation between urinary N-acetyl-β-D-glucosamindase (NAG)/creatinine levels, depleted uranium concentration in the kidney, and the depleted uranium dose (Fukuda et al. 2006). The investigators suggested that urinary NAG/creatinine levels are a useful biomarker to assess kidney damage and estimate depleted uranium intake.

Toxicogenomic studies have sought to identify biomarkers that can be used to evaluate uranium-related kidney damage by examining alterations in gene or protein expression patterns in uranium-exposed renal cells and alterations in levels of urinary proteins (Malard et al. 2009; Prat et al. 2005, 2011). Prat et al. (2005) identified a "transcriptomic fingerprint" of 18 genes that form the core mRNA response to uranium in renal cells. Additionally, they identified a set of five modulated genes/proteins that could potentially be used as biomarkers of effects: actin-β, tubulin-α, high mobility group protein 1 (HMGB1), protein 14-3-3, and heat shock protein (hsp) 90. A subsequent *in vitro* study by this group (Prat et al.

2011) found repression of the SPP1 gene coding for osteopontin in human kidney HK2 cells; osteopontin levels were inversely related to the uranium level. Urinary osteopontin levels were also decreased in uranium workers with urinary uranium levels >30 µg/L or individuals with chronic exposure to uranium in drinking water (Prat et al. 2011). The investigators cautioned that it is not known if the decreased osteopontin levels are specific to uranium toxicity and noted that interindividual variability in urinary osteopontin levels is quite high. In a study of rats injected with uranyl nitrate (Malard et al. 2009), 14 proteins were shown to be modulated by uranium exposure. A number of the proteins have been shown to be altered in response to kidney damage. These protein alterations included increases in the urinary levels of albumin, α-1-antiproteinases, transthyretin, ceruloplasmin, and transferrin and decreases in urinary epidermal growth factor, contraspsin-like protease inhibitor 3, and pancreatic α-amylase.

Very high doses of uranium may interfere with liver function in humans (Pavlakis 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* (Agency for Toxic Substances and Disease Registry 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. 1998), should be considered for evaluating subjects in future studies.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Co-administration of uranium (5 mg/kg uranyl acetate dehydrate administered via subcutaneous injection) and melatonin (10 or 20 mg/kg administered via intraperitoneal injection) resulted in a decrease in uranium-induced kidney damage (Bellés et al. 2007). A significant reduction in the uranium-induced increase in urine volume and a reduction in the severity of renal tubular necrosis were observed. No information was located regarding the modulation of the toxicity of uranium by other chemicals or vice versa.

3.10 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 result in reduced detoxification or excretion of uranium, or compromised function of organs

affected by uranium. Populations who are at greater risk due to their unusually high exposure to uranium are discussed in Section 6.7, Populations with Potentially High Exposures.

Populations susceptible to uranium toxicosis would include people with impaired renal function or renal disease. 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 3.6.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing 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 and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to uranium:

Began D. 2002. Dermatologic principles. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, 432-440.

Goans RE. 2007. Medical management of radiation incidents. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders, 1467-1485.

NCRP. 2010. Management of persons contaminated with radionuclides: Handbook. NCRP Report No. 161. National Council on Radiation Protection and Measurements, 128-137, 176-236. http://www.ncrponline.org/Publications/161press.html. February 11, 2010.

3.11.1 Reducing Peak Absorption Following Exposure

No specific recommendations have been reported for reducing the peak absorption following acute inhalation or oral exposure to uranium. The only specific recommendation reported regarding reducing absorption of uranium following exposure is to not wash the skin with water following dermal exposure to dusts of pure uranium because it will ignite or explode when contacted by water (Began 2002). Thus, it is recommended that any residual metal should be removed with forceps, gauze, or towels and stored in mineral oil.

Houpert et al. (2001, 2004) investigated the use of chelating agents to decrease the transfer of uranium from a wound to blood. Wound contamination with uranium was simulated by an intramuscular injection of 0.66 µg U as uranyl nitrate or 63 µg U as industrial-grade uranium peroxide in the hind leg of rats (Houpert et al. 2001). Following exposure to uranium, the rats received an intramuscular or intraperitoneal injection or carballylic amido bis phosphonic acid (CAPBP). A significant increase in the amount of uranium retained at the wound site was found following the intramuscular injection of CAPBP; significant reductions in uranium levels in the kidneys, femur, carcass, and urine were also observed. Intraperitoneal administration of CAPBP did not significantly reduce uranium absorption or alter uranium tissue levels. In the second study (Houpert et al. 2004), the hind leg skin was incised and industrial-grade uranium peroxide was deposited in the underlying muscle; the wound was then covered for 1 hour with a dressing or paste composed of carboxymethylcellulose-based hydrocolloids, which are highly absorbant; in two groups, the paste was mixed with CAPBP or ethane-1-hydroxy-1,1-bisphosphonate. Although the dressing and paste were effective in decreasing the amount uranium at the wound site and uranium levels in the kidneys, adding the chelating agent to the paste did not alter its efficiency.

3.11.2 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® (sodium 4,5-dihydroxybenzene-1,3-disulphonate) 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 after exposure to uranium (Domingo et al. 1992). Bicarbonate treatment is also limited to very near-term exposures. Another study that tested Tiron® alone and in conjunction with either DTPA or ethylenediamine-N,N'-bis(2-hydroxyphenylacetic acid) (EDHPA) 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).

Other studies have reported the efficiency of other chelating agents on reducing toxicity or tissue levels of uranium. Administration of catechol-3,6-bis-(methyleiminodiacetic acid) (CBMIDA) or ethane-1-hydroxy-1,1-bisphosphonate (EHBP) for 28 days after an intramuscular injection of 2 mg U/kg resulted in a reduction in mortality and decreases in uranium levels in the kidney, bone, and liver (Fukuda et al. 2005). Fukuda et al. (2009) also demonstrated that oral or intraperitoneal administration of CBMIDA for 6 days significantly increased excretion of uranium and decreased tissue uranium levels in rats administered 8 mg/kg depleted uranium via intraperitoneal or intramuscular injection.

Administration of bicarbonate for 3 days following an intramuscular injection of 4 mg/kg depleted uranium did not result in a significant reduction in uranium tissue levels or improvement in renal function in rats (Fukuda et al. 2008). However, co-administration of bicarbonate with the chelating agent, deferiprone, resulted in decreased uranium tissue levels and increased urinary uranium excretion compared to groups of depleted uranium exposed rats administered bicarbonate only or deferiprone only. Co-administration of bicarbonate and 4,6-dimethyl-1-hydroxyprimidin-2(1H)-one resulted in an increase in uranium excretion but did not affect tissue levels or organ function. Bicarbonate did not increase the efficiency of CBMIDA and was found to decrease the efficiency of EHBP.

Administration of a 500 mg/kg oral dose or 50 mg/kg subcutaneous dose of bisodic etidronate immediately following administration of a 170 mg U/kg dose of uranyl nitrate hexahydrate resulted in a 50% reduction in mortality and an improvement in the uranium-induced reduction in growth cartilage width, metaphyseal bone volume, and metaphyseal bone activity in male Balb/c mice (Bozal et al. 2005). Similarly, oral or subcutaneous administration of EHBP (Martinez et al. 2000, 2003) or bisodic etidronate (Martinez et al. 2003) immediately following administration of a single 170 mg U/kg as uranyl nitrate oral dose resulted in a decrease in mortality and a lessening of the severity of kidney lesions.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No studies that examined methods for interfering with the mechanisms of action were identified.

3.12 ADEQUACY OF THE DATABASE

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

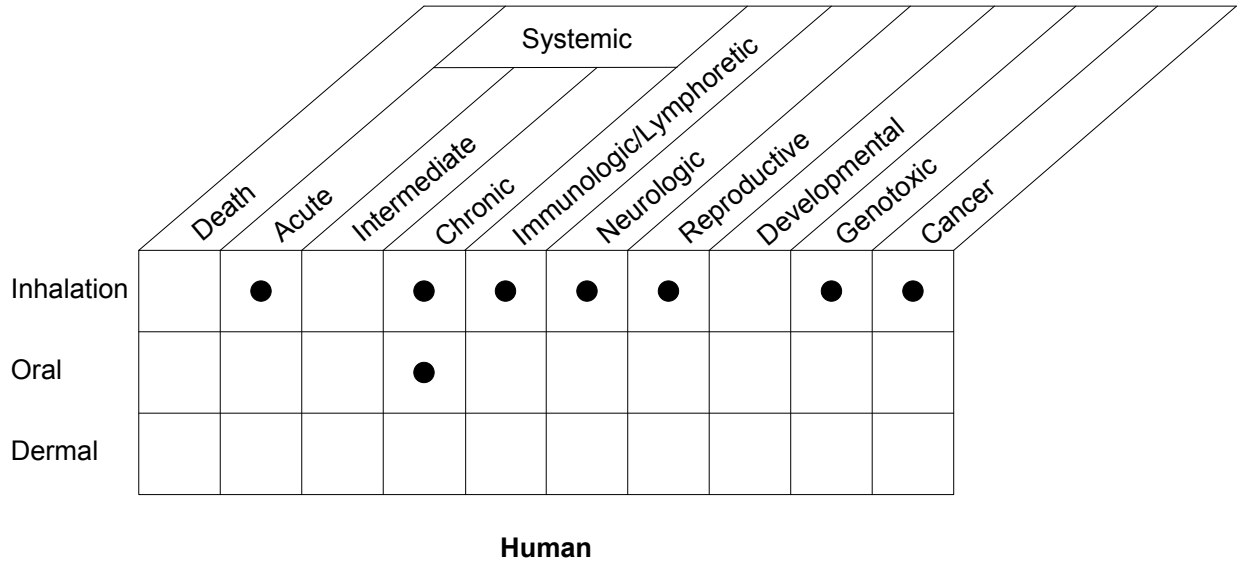
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

3.12.1 Existing Information on Health Effects of Uranium

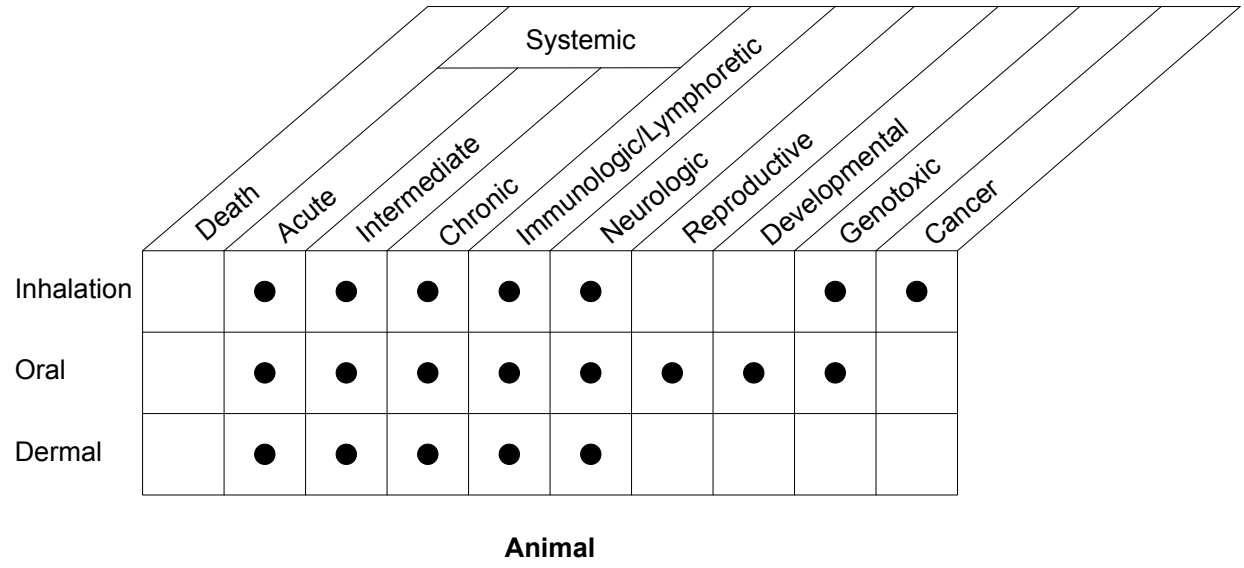
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to uranium are summarized in Figure 3-11. The purpose of this figure is to illustrate the existing information concerning the health effects of uranium. Each dot in the figure indicates that one or more 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* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-11 depicts the existing health effects information on uranium for a specific route and duration of exposure. There are limited data on uranium toxicity in humans following inhalation or oral exposure; no dermal exposure studies were identified. 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. 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. Oral studies are limited to several ecological studies of communities exposed to elevated uranium in drinking water. Although the studies did find significant associations, particularly for biomarkers of renal

Figure 3-11. Existing Information on Health Effects of Uranium



Human



Animal

● Existing Studies

dysfunction, the studies do not provide reliable dose-response data. Information on the systemic effects of uranium through the inhalation, oral, and dermal routes of exposure are available in a number of animal species. Several studies have examined the neurological, reproductive, and developmental toxicity of uranium following oral exposure. Reproductive and developmental end points have not been examined following inhalation or dermal exposure. Non-specific neurological symptoms have been reported in animals exposed via the inhalation or dermal routes to lethal concentrations of uranium. The carcinogenicity of uranium has been investigated in inhalation studies, but not in oral or dermal studies.

3.12.2 Identification of Data Needs

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 (Lu and Zhao 1990) and an intentional ingestion of approximately 131 mg U/kg as uranyl acetate (Pavlakis et al. 1996), resulted in renal toxicity. Acute-duration studies in animals mainly examined lethality. Inhalation acute-duration lethality studies in rats and guinea pigs are available for uranium hexafluoride for short durations (<2 hours) (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. Additionally, there are acute oral studies examining systemic toxicity (Ozmen and Yurekli 1998), neurological effects (Briner 2009; Briner and Murray 2005), and developmental toxicity (Domingo et al. 1989c; Pujadas Bigi et al. 2003). The inhalation studies were inadequate for derivation of an MRL because the exposure durations were very short. An acute oral MRL was derived based on a developmental toxicity study (Domingo et al. 1989c). Acute-duration studies that define threshold values for renal toxicity by the inhalation and oral routes 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.

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. A number of animal studies have evaluated the toxicity of various uranium compounds in a number of animal species (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 insoluble and soluble uranium compounds (see Chapter 2 and Appendix A); however, additional inhalation studies are needed to better define concentration-response relationships. 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. Inconsistent results were found in the rabbit studies (Gilman et al. 1998b, 1998c), which the investigators attributed to a possible subclinical infection. No threshold for the histopathological effects was observed; the lowest dose tested in the rats was considered a minimal effect and was used to derive an oral MRL for this duration (see Chapter 2 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, and to validate the results of the rabbit studies. No reliable studies examining the oral toxicity of insoluble uranium compounds were identified; studies providing dose-response data would be useful for establishing an MRL for insoluble compounds. 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; Lopez et al. 2000; 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 small number of occupational exposure studies have examined renal toxicity. No evidence of renal toxicity was reported in workers exposed to relatively low concentrations of insoluble uranium compounds (Eisenbud and Quigley 1956). However, significant increases in urinary biomarkers of renal dysfunction were observed in workers exposed to ammonium diuranate (Thun et al. 1985). Future studies of uranium workers should include exposure assessments and measurement of sensitive biomarkers of renal damage. 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). Studies of underground uranium miners have not yet accounted for confounding by diesel engine exhaust or crystalline silica dust, especially freshly cracked silica dust, which was in high concentrations in mine air; and have been identified as carcinogens. A small number of studies have examined the chronic toxicity of inhaled uranium in animals. Studies involving exposure to soluble uranium compounds have identified the kidney as the most sensitive target (Stokinger et al. 1953) and were used to derive a chronic-duration MRL for soluble compounds. Data for insoluble compounds suggest that at low concentration and long exposure duration (≥3.5 years), the lung may be a more sensitive target than the kidney (Leach et al. 1970). However, the lung effects may be due to radiotoxicity rather than chemical toxicity. Additional mechanistic studies are needed to identify the causative agent. The data were considered adequate for derivation of an MRL for insoluble uranium compounds; however, additional studies are needed to better define the concentration-response relationship for pulmonary and renal effects. Several ecological studies have examined the possible association between elevated levels of uranium in drinking water and impaired kidney function (Kurttio et al. 2002, 2006a; Limson Zamora et al. 1998, 2009; Mao et al. 1995; Seldén et al. 2009). Several studies have sound significant association. A common limitation of the studies is a lack of accurate dose-response data. A series of studies in rats and dogs have examined the chronic toxicity of a variety of uranium compounds (Maynard and Hodge 1949; Maynard et al. 1953). The dog studies were not considered suitable for MRL derivation because only two dogs were exposed to each dose level. Although the rat studies tested an adequate number of animals and included histopathological examination of major tissues and organs, including the kidneys, a chronic-duration oral MRL could not be derived for uranium. Oral exposure studies examining a variety of end points, including sensitive end points of renal toxicity, are needed for soluble and insoluble uranium compounds. No chronic-duration dermal toxicity studies were identified in humans or animals.

A number of epidemiological studies are available for workers exposed to uranium (miners, millers, processors). A number of studies reported death from lung cancers from occupational inhalation exposure of mine workers (Archer et al. 1973a; Gottlieb and Husen 1982; Lundin et al. 1969; Samet et al. 1984a, 1986); however, the 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 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 et al. 1983). There are limited animal data on the carcinogenicity of uranium following inhalation exposure and no oral or dermal exposure studies. Pulmonary neoplasms were observed in dogs (Leach et al. 1973) and rats (Mitchel et al. 1999).

Genotoxicity. Limited data exist regarding *in vivo* genotoxicity in humans following exposure to uranium. The only cases in which there were documented exposures to uranium are those of the Gulf War veterans who retained depleted uranium embedded fragments (McDiarmid et al. 2000, 2001a, 2004b, 2007, 2009). Prospective tests for clastogenicity and mutations in blood cells from this group yielded inconsistent results that led the investigators to conclude that the body of evidence in that cohort showed relatively weak genotoxic effects from uranium exposure. Future assessments are unlikely to provide key new information. Other assessments of small cohorts presumed to have been exposed to depleted uranium provided positive evidence of clastogenicity (Krunić et al. 2005; Milačić 2008; Milačić and Simić 2009; Milačić et al. 2004; Schröder et al. 2003). Studies of populations in areas with high levels of uranium in drinking water or soil would be valuable. *In vivo* studies in animals provided positive evidence of genotoxicity after inhalation and oral exposure to depleted uranium (Hao et al. 2009; Miller et al. 2010; Monleau et al. 2006a). Miller et al. (2010) also showed that implantation of depleted uranium pellets in male mice for 7 months followed by mating with untreated females resulted in transmission of genetic damage to somatic cells of offspring; the exact mechanism by which this occurred is not known, so further studies in this area are warranted. In addition, similar studies in mice exposed to uranium by routes relevant to general population exposure (contaminated drinking water or food) would be valuable. Studies of genotoxicity *in vitro*, both with mammalian cells (LaCerte et al. 2010; Lin et al. 1993; Miller et al. 2002a, 2002b, 2003; Stearns et al. 2005; Thiébault et al. 2007; Wise et al. 2007) and prokaryotic organisms (Miller et al. 1998a; Yazzie et al. 2003) have yielded positive results. Studies with HOS cells showed that depleted uranium induced *de novo* genomic instability in the cells, which led to delayed reproductive death for many generations (Miller et al. 2003). Further studies aimed at elucidating the mechanism by which this can occur are needed. Some studies showed differences in genotoxic capacity between water-soluble and -insoluble uranium compounds (LaCerte et al. 2010; Wise et al. 2007). The investigators speculated that the difference may be related to differences in kinetics between the two types of uranium compounds; research in this area would be helpful. A study in CHO cells showed that uranium can form adducts with DNA (Stearns et al. 2005). Further research in this area can provide information regarding possible sensitive biomarkers for uranium exposure. There is an apparent knowledge gap between the positive findings of genotoxicity in *in vitro* and *in vivo* studies and the

predominantly negative findings of carcinogenicity studies. Additional studies are needed to address this data deficiency.

Reproductive Toxicity. Existing human data from male uranium miners, millers, and processors (Muller et al. 1967; Waxweiler et al. 1981b; Wiese and Skipper 1986) and from men exposed to depleted uranium in the Gulf War via retained metal embedded fragments (McDiarmid et al. 2000, 2001a, 2004b, 2007, 2009) have not suggested adverse uranium-induced reproductive effects. The Gulf War veterans were subjected to longitudinal analyses of sex hormone levels in blood and sperm parameters; however, no assessments of fertility have been conducted. It would be helpful to have that information, if available. Exposure to uranium reduced fertility in male mice (Llobet et al. 1991) and male rats (Linares et al. 2005) exposed via the drinking water. In the former study, reduced fertility was associated with reduced spermatozoa counts; in the latter, there were morphological alterations in Sertoli or germinal cells. Fertility was not affected in mice dosed with uranium by gavage (Paternain et al. 1989) or in a 2-generation reproductive toxicity study in rats implanted depleted uranium pellets (Arfsten et al. 2009). Differences in exposure routes may have played a role in the difference results obtained. Clearly, drinking water studies are more relevant to potential exposures of the general population than exposures by gavage or through an embedded uranium pellet. Of the four studies mentioned above (Arfsten et al. 2009; Linares et al. 2005; Llobet et al. 1991; Paternain et al. 1989), urinary uranium, as a biomarker of exposure, was only monitored by Arfsten et al. (2009). Studies are also available that reported that exposure to uranium altered ovarian folliculogenesis in mice (Arnault et al. 2008; Feugier et al. 2008; Kundt et al. 2009; Raymond-Whish et al. 2007). The study conducted by Raymond-Whish et al. (2007) reported slight alterations in ovarian folliculogenesis in mice administered doses as low as 0.39 µg U/kg/day. These authors also reported estrogenic effects in mice treated with 5 µg U/kg/day. Since these doses are orders of magnitude lower than those used in other studies, it would be reassuring if the findings of Raymond-Whish et al. (2007) can be replicated by other laboratories. A study in rats reported that enriched uranium, but not depleted uranium, increased serum testosterone and the expression of genes involved in steroidogenesis (Grignard et al. 2008). In addition, enriched uranium significantly increased the expression of transcription factors involved in the regulation of steroidogenic genes. This is the only study available that compared the effects of enriched versus depleted uranium on some reproductive end points. Additional studies comparing the effects of depleted and enriched uranium on other reproductive end points (i.e., fertility, sperm parameters, microscopic morphology of reproductive organs, estrogenicity, levels of sex hormones) would be valuable to distinguish between chemical and radiological activity.

Developmental Toxicity. There are no studies of developmental effects in humans with documented exposure to uranium. Several reports have been published regarding increased incidence of teratogenicity in populations presumed to have been exposed to depleted uranium; this subject was reviewed by Hindin et al. (2005). It should be noted that all of the reports lack documentation of individual exposure to depleted uranium, some reports lacked methodologically rigorous investigation (like exposure to other chemicals and other confounders), and in the incidences of birth defects between supposedly exposed and nonexposed groups was not statistically significant in other reports. Yet, Hindin et al. (2005) concluded that the evidence linking exposure to depleted uranium and birth defects, albeit imperfect, indicates a high probability of substantial risk. Studies could be conducted of offspring of women living in areas with documented high uranium in the drinking water or the soil to evaluate possible associations between uranium and birth defects in humans.

Maternal exposure to uranium during pregnancy has induced fetotoxicity, teratogenicity, and reduced neonatal viability in mice (Domingo et al. 1989b, 1989c; Paternain et al. 1989). An issue that is not totally clear is whether this occurs at doses not causing maternal toxicity. An additional issue that has not been explored is evaluation of the contribution of gestational exposure versus lactational exposure to the uranium-induced decreased neonatal viability. Valuable information could be collected to address this question by conducting cross-fostering studies. Gestational exposure to uranium did not affect developmental landmarks in mice (Domingo et al. 1989b) or rats (Sánchez et al. 2006). However, in rats, perinatal exposure altered the results of some neurobehavioral tests conducted in the offspring (Houpert et al. 2007a; Sánchez et al. 2006). Histological examination of different brain areas of the offspring as well as measurements of neurotransmitters could provide information regarding possible mechanisms involved in the neurobehavioral effects of perinatal exposure to uranium. In contrast with the findings of Houpert et al. (2007a) and Sánchez et al. (2006), a study in rats implanted depleted uranium pellets for 120 days before mating reported no significant alterations in neurobehavioral tests conducted on the offspring on postnatal days 4–63 (Arfsten et al. 2009). This 2-generation reproductive study also did not report significant alterations in viability of the F1 generation or in histology of selected organs or sperm parameters on postnatal day 120. Different results between studies are not totally unexpected since exposure protocols were different. Sánchez et al. (2006) exposed only females via drinking water for 4 weeks, Houpert et al. (2007a) exposed males and females via drinking water for 3 months, and Arfsten et al. (2009) implanted uranium pellets in both males and females. Information regarding uranium body burdens in the parental generation, such as urinary uranium levels, would be helpful for comparing studies with differing exposure protocols. Studies also showed that in mice, gestational exposure to uranium can alter ovarian folliculogenesis in the female offspring (Arnault et al. 2008; Raymond-Whish

et al. 2007). In one of these studies (Raymond-Whish et al. 2007), effects occurred at doses much lower than those tested in any other animal study. It would be useful to try to replicate these findings. Neonatal exposure of rats to uranium interfered with tooth eruption and development (Pujadas Bigi and Ubios 2007; Pujadas Bigi et al. 2003), but only one dose level was tested so that a NOAEL was not defined. Studies designed to define a NOAEL and to allow construction of a dose-response curve would be helpful. Recently, it was shown that paternal exposure to uranium via implantation of depleted uranium pellets resulted in transmission of genetic damage to somatic cells of unexposed offspring (Miller et al. 2010). The investigators noted that studies investigating the effects of depleted uranium exposure on germ cell mutagenesis and direct DNA damage to sperm are being completed. It would be valuable if similar studies are conducted with male mice exposed by a route more relevant to exposures of the general population such as via contaminated drinking water or food.

Immunotoxicity. There are limited data on the immunotoxic potential of uranium. Epidemiology studies that examined white blood cell levels or mortality from immune disease have not reported adverse effects following inhalation, oral, or dermal exposure (Archer et al. 1973b; Checkoway et al. 1988; Cragle et al. 1988; Keane and Polednak 1983; NIOSH 1987; Polednak and Frome 1981; Vich and Kriklava 1970). 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. In general, studies of uranium workers have not provided evidence of adverse neurological effects, although tests to detect subtle neurological alterations were not conducted (Carpenter et al. 1988; Cragle et al. 1988; Hadjimichael et al. 1983; Kathren and Moore 1986; NIOSH 1987; Polednak and Frome 1981; Reyes et al. 1984; USNRC 1986). Workers were presumed to have been

exposed mainly by the inhalation and dermal routes. Longitudinal assessments of Gulf War veterans who retained depleted uranium fragments and were excreting elevated urinary levels of uranium years after the first exposure provided inconsistent results in neurobehavioral tests (McDiarmid et al. 2000, 2001a, 2004b, 2007, 2009). Surveillance of this group of subjects should continue to try to identify potentially late-appearing effects or normal aging signs that might manifest prematurely. No information was located regarding neurological effects in humans exposed orally to uranium. Early inhalation studies in animals exposed to dusts of fluoride salts of uranium reported frank neurological effects, but did not consider the possible contribution of fluoride (Dygert 1949a; Rothstein 1949a). More recent oral studies in animals have reported changes in biochemical parameters, including levels of neurotransmitters and their metabolites, in various areas of the brain following acute- and intermediate-duration exposure to uranium (Briner 2009; Briner and Murray 2005; Bussy et al. 2006). Studies also have examined neurobehavioral parameters following exposure to uranium; some reported neurobehavioral alterations (Briner 2009; Briner and Murray 2005; Houpert et al. 2005, 2007b), while others did not (Arfsten et al. 2007; Belles et al. 2005). Studies are needed that conduct morphological, electrophysiological, and biochemical evaluations in the same animals following exposure to uranium to shed light into possible mechanism(s) of action for uranium-induced neurological effects. No studies were located that examined neurological parameters in animals following chronic-duration exposure to uranium. Such studies would provide information regarding long-term, low-level exposure as could occur to populations exposed to excessive uranium in the drinking water or through consumption of food grown in areas with elevated concentrations of uranium in the soil.

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; Checkoway et al. 1988; Cragle et al. 1988; Gottlieb and Husen 1982; Hadjimichael et al. 1983; Lundin et al. 1969; NIOSH 1987; Polednak and Frome 1981; Samet et al. 1984a, 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. Animal studies provide strong evidence that the kidney is the most sensitive target of uranium toxicity. Alterations in sensitive biomarkers of renal dysfunction have been observed in workers exposed

to airborne soluble uranium compounds (Thun et al. 1985) and in residents consuming drinking water with elevated uranium levels (Limson Zamora et al. 1998, 2009; Mao et al. 1995). However, occupational exposure studies of workers exposed to insoluble uranium (as reviewed by Eisenbud and Quigley 1956) and ecological drinking water studies (Kurttio et al. 2006a; Seldén et al. 2009) have not found significant kidney effects. Most of these studies provide limited dose-response data, and studies examining sensitive end points of renal toxicity, as well as other potential targets of toxicity, are needed to assess the relative sensitivity of humans to uranium toxicity as compared to animal species, which are used to derive MRLs for uranium. Also, simple and accurate monitoring methods should be developed for workers that would determine the relationship among atmospheric concentration, particle size, distribution, physical properties of the uranium aerosol, body burden, and excretion rates and pathways. The use of depleted uranium munitions by the military has resulted in the potential uranium exposure to military personnel and civilians; additional research regarding the health effects of acute-duration inhalation exposure to depleted uranium would be useful to assess the potential for toxicity. These studies should include toxicological end points, lung doses, metabolic fate, and techniques to detect and monitor lung exposures.

Biomarkers of Exposure and Effect.

Exposure. Because uranium is primarily excreted in the urine following inhalation, oral, or dermal exposure, measurement of urine uranium levels can accurately estimate uranium body burden (Ballou et al. 1986; Cooper et al. 1982; Downs et al. 1967; Leach et al. 1984; McDiarmid et al. 1999b; Morrow et al. 1982a; Stradling et al. 1984, 1987; West and Scott 1969; Wrenn et al. 1985). Several methods have been developed for chemical detection (e.g., fluorimetry and kinetic phosphorescence analysis) and radiological detection (e.g., inductively coupled plasma mass spectrometry [ICP-MS] and alpha spectroscopy). Although correlations between uranium intake and urinary levels have been reported, additional studies are needed that would allow for the development of a biokinetic model, which would allow estimation of uranium intake based on urinary uranium levels.

Uranium content in soft tissue and bone could also be used as biomarkers of exposure to uranium (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.

Effect. Currently, there are no available biomarkers for specific exposure to the metallotoxic or radiotoxic effects of uranium. Although the kidney is the most sensitive target of uranium toxicity, biomarkers of renal dysfunction such as β_2 microglobulin, protein HC, and retinol binding protein are not specific to uranium. Additional studies are needed to correlated these alterations with renal damage and establish dose-response relationships.

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. Most of the available research on methods for reducing the toxic effects of uranium have focused on the effectiveness of chelating agents on reducing the accumulation of uranium in the body (Bozal et al. 2005; Domingo et al. 1992; Fukuda et al. 2005, 2009; Martinez et al. 2000, 2003; Ortega et al. 1989a; Stradling et al. 1991). Several agents including Tiron, CBMIDA, EHBP, and bisodic etidronate have significantly reduced tissue uranium levels, decreased renal toxicity, and increased survival when the chelating agent was administered shortly after exposure. The effectiveness of bicarbonate in facilitating the excretion of uranium has also been investigated (Cooper et al. 1982; Fisher et al. 1991; Fukuda et al. 2008). However, few studies have investigated the effectiveness of these agents when they are administered after long-term uranium exposure and more studies are needed. No studies investigating methods for reducing peak absorption following inhalation or oral exposure were identified. Houpert et al. (2001, 2004) explored the use of dressings with or without chelating agents on decreasing the absorption of uranium from wounds. No studies researching methods for interfering with the toxic mechanisms of action were identified. Further research is needed

to validate, refute, or refine method(s) for reducing the body burden, particularly following long-term exposure, and research is needed on methods for decreasing absorption and interfering with the mechanism of toxicity.

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

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 (Lu and Zhao 1990) or intentionally (Pavlakis et al. 1996). Because children undergo periods of rapid bone growth and remodeling and uranium is stored in bone, there is a need to examine the potential toxicity of uranium to bone. However, few studies have examined this end point and additional studies are needed.

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 on the absorption of various forms of uranium in young animals would be useful. 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 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies are examining possible kidney toxicity in residents living near uranium mining sites, genotoxicity of depleted uranium, and adverse health outcomes in Gulf War veterans exposed to depleted uranium.

The Congressionally-mandated Navajo Uranium Assessment and Kidney Health Project is a joint Department of Energy (DOE), EPA, and ATSDR effort with three foci: (1) conducting medical monitoring; (2) completing safe water projects; and (3) studying the potential effects of heavy metals, including uranium, on pregnant women and their infants. ATSDR, in collaboration with the Indian Health Service and the Navajo Nation hospital and clinic staff, will conduct case control studies of health risks faced by individuals residing near mill sites or abandoned mine sites. The study will include a birth cohort study to address the potential association between environmental exposure to a suite of heavy metals, including uranium, and both maternal health and reproductive birth outcomes. The birth cohort study is being conducted by the University of New Mexico under a cooperative research agreement with ATSDR (EPA 2013a).

The U.S. Department of Energy's Lawrence Berkeley National Laboratory is currently developing a sequestering agent that could be administered following exposure to actinides, such as plutonium, americium, uranium, and neptunium, and result in increased excretion of the actinide contaminants.