2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO URANIUM IN THE UNITED STATES

Uranium is an alpha-emitting, radioactive, heavy metal that occurs naturally in nearly all rocks and soils. Twenty-two isotopic forms of uranium have been identified, mainly associated with nuclear reactor operations or high-energy physics experiments; the most prevalent isotopes found in the environment are the three naturally-occurring isotopes: ^{234}U, ^{235}U, and ^{238}U. Most uranium isotopes undergo decay by alpha emission, a few undergo beta emission, and several isotopes, including ^{238}U, can also undergo spontaneous fission. ^{238}U decays through 16 radioactive progeny, including ^{234}U, to reach stable lead-206 (^{206}Pb), while ^{235}U decays through 13 radioactive progeny to reach stable ^{207}Pb. The rate of decay (or half-life) for most uranium isotopes is long; the half-lives of ^{238}U, ^{235}U and ^{234}U are $4.5x10^9$, $7.0x10^8$ and $2.5x10^5$ years, respectively. Since the activity of a given mass of uranium depends on the mass and half-life of each isotope present, the greater the relative abundance of the more rapidly decaying ^{234}U and ^{235}U, the higher the specific activity. Naturally occurring uranium is an isotopic mixture containing 99.284% ^{238}U, 0.711% ^{235}U, and 0.005% ^{234}U by mass (49% ^{238}U, 2% ^{235}U, and 49% ^{234}U by radioactivity) and has a specific activity of 0.68 μCi/g. The industrial process of enrichment separates natural uranium into enriched uranium (increased percentage of ^{235}U) and depleted uranium (decreased percentage of ^{235}U). The process of enrichment also increases the percentage of ^{234}U (thus, enriched uranium is more reactive); depleted uranium has a decreased percentage of ^{234}U and is less radioactive. Uranium enrichment for commercial nuclear energy produces uranium that contains about 3% ^{235}U by activity. Uranium enrichment for other purposes, including nuclear weapons production, can produce uranium containing as much as 97.3% ^{235}U and having a higher specific activity (~50 μCi/g). Depleted uranium is the byproduct of the enrichment process. Depleted uranium has even less specific activity (0.33 μCi/g) than natural uranium.

The average concentration of uranium in U.S. soils is about 3 ppm (2 pCi/g). Some parts of the United States, particularly the western portion, exhibit higher-than-average uranium levels due to natural geological formations. Most uranium ores contain between 0.2 and 5% uranium by weight; however, levels as high as 22% have been reported in the Athabasca Basin region of Canada. Anthropogenic sources of uranium include uranium mining and milling, uranium conversion and enrichment, uranium fuel fabrication, nuclear weapons production, production of phosphate fertilizers from phosphate rocks containing uranium, and the improper disposal of uranium mine tailings. Essentially no uranium is

released from nuclear power plants because of the fuel assembly design and the chemical and physical nature of the uranium oxide fuel.

The general population is exposed to uranium via ingestion of food and drinking water and inhalation of air, with food being the primary contributor to body burden. The daily intake of uranium from food sources ranges from 0.6 to 1.0 pCi/day (0.9–1.5 µg/day). Uranium from soil is not taken up by plants, but rather is adsorbed onto the roots. Thus, the highest levels of uranium are found in root vegetables, primarily unwashed potatoes. Populations living near uranium mills or mines or other areas with elevated uranium in soil may be exposed to higher levels of uranium from locally grown vegetables. Uranium levels in drinking water vary widely, with a mean population-weighted average of 0.8 pCi/L. Compared to the ingestion route, the intake of uranium via inhalation is small; intakes range from 0.0007 to 0.007 pCi/day (0.001–0.01 µg/day).

Uranium is poorly absorbed following inhalation, oral, or dermal exposure and the amount absorbed is heavily dependent on the solubility of the compound. The site of deposition of inhaled particles in the respiratory tract also influences absorption. The more soluble compounds are more likely to be absorbed into the blood at the alveolar level within days. The less soluble compounds are more likely to remain in the lung tissue and associated lymph nodes either for weeks (uranium trioxide, uranium tetrafluoride) or years (uranium dioxide, triuranium octaoxide), resulting in significant pulmonary retention in inhalation-exposure toxicity and a greater dose of alpha radiation. Absorption efficiencies of 18–40 and 23% have been reported in animals exposed to uranium hexafluoride or uranium trioxide aerosols, respectively. Following oral exposure, <0.1–6% of the uranium is absorbed, depending on the solubility of the uranium compound. Following dermal application of uranyl nitrate, 0.4% of the dose was absorbed through the skin of hairless rats. Damage to the skin resulted in substantially higher absorption efficiencies. Transdermally absorbed uranium and uranium released from embedded fragments is expected to behave identically to uranium compounds absorbed through the lungs and the gastrointestinal tract. Regardless of solubility, a portion of uranium quickly reaches the systemic circulation. Uranium is usually found in compounds that can break down and recomplex to form other compounds. In body fluids, tetravalent uranium is likely to oxidize to the hexavalent form, followed by formation of the uranyl ion. Uranium generally complexes with citrate, bicarbonates, or protein in plasma. 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, primarily the bone, liver, and kidney. The retention half-time for uranium in bone following inhalation exposure to soluble uranium compounds is 70–200 days. The main sites of long-term retention for inhaled insoluble compounds that are deposited in the deep respiratory tract are the lungs and

pulmonary lymph nodes. The normal adult body burden is approximately 90 μg of which 66% is found in bone, 16% is in the liver, 8% is in the kidneys, and 10% is in other tissues.

2.2 SUMMARY OF HEALTH EFFECTS

The following discussion of the chemical and radiological health effects of uranium is divided into the three groupings of uranium isotope mixtures (natural uranium, enriched uranium, and depleted uranium) and the various compounds in which uranium is usually found. The health effects of daughter radioactive elements (radium and radon) are addressed in other toxicological profiles (consult the ATSDR toxicological profiles for radium and radon for more information regarding these radioactive elements). The preponderance of the available toxicity data comes from animal studies of natural uranium; studies over the last 20 years have also evaluated the toxicity of enriched uranium in animals and depleted uranium in military personnel with embedded depleted uranium fragments and in animals. Comparisons across studies provide evidence that the chemical action of all isotopes and isotopic mixtures of uranium is identical, regardless of the specific activity, because chemical action depends only on chemical properties. Thus, the chemical toxicities of natural, depleted, and enriched uranium are identical. Some recent studies also suggest that exposure to enriched uranium can also result in radiotoxic effects.

Natural Uranium. Current evidence from animal studies suggests that the toxicity of uranium is mainly due to its chemical damage to kidney tubular cells following exposure to soluble uranium compounds and the respiratory tract following chronic inhalation exposure to insoluble uranium compounds. Other potential targets of toxicity include the reproductive system and the developing organism. There are limited data on the renal toxicity of uranium following inhalation exposure in humans. A number of studies found no alterations in mortality due to renal disease in uranium workers. An autopsy study of long-time workers exposed to low levels of uranium did not find evidence of renal injury years after exposure termination. However, a study of uranium mill workers exposed to uranium found evidence of renal dysfunction (β-2-microglobinuria, aminoaciduria); the severity and incidence of the effects appeared to be related to exposure duration. Several epidemiology studies have found associations between nonspecific parameters of renal dysfunction (e.g., urine levels of albumin, β_2-microglobulin, glucose, and protein HC) and elevated uranium levels in drinking water. These studies did not find overt signs of toxicity and in many cases, the biomarkers of renal dysfunction were within the normal range. Although most of the epidemiology studies provided information on uranium levels in the drinking water, there was often a large range of exposure levels; thus, the human oral exposure studies do not provide reliable dose-response data.

Renal effects have been observed in a number of animal species exposed to various uranium compounds. The observed effects have primarily involved damage to the proximal tubules and have been observed following inhalation, oral, or dermal exposures. The majority of the data on the renal toxicity of uranium come from a collection of experiments conducted in late 1940s and early 1950s. The results of these studies demonstrate compound- and species-related differences in toxicity. Soluble uranium compounds (e.g., uranyl nitrate, uranyl fluoride, uranium hexafluoride, and uranium tetrachloride) are more toxic than insoluble uranium compounds (e.g., uranium dioxide, uranium peroxide, uranium trioxide, and triuranium oxtaoxide). Renal effects have been observed in animals exposed to aerosols of soluble uranium compounds at concentrations of ≥0.13 mg U/m^3 for intermediate durations. However, no renal effects were observed in animals exposed to 1.0 mg U/m^3 as insoluble compounds; the lowest-observed-adverse-effect level (LOAEL) was 8.2 mg U/m^3. These data suggest that soluble compounds are at least 5 times more toxic than insoluble compounds. The difference in toxicity is likely due to the more efficient absorption of soluble uranium compounds. Of the animals tested in intermediate-duration inhalation studies, dogs and rabbits are the most sensitive followed by rats, mice, and guinea pigs. The severity of renal lesions increases with increasing exposure concentrations; very slight renal tubular damage is observed at low concentrations and marked degeneration and necrosis are observed at higher concentrations. The available data on the oral and dermal toxicity of uranium are more limited than by the inhalation route. Acute-, intermediate-, and chronic-duration oral studies in laboratory animals (rats, mice, rabbits, and dogs) provide strong support for identifying the kidney as a sensitive target of uranium toxicity. Acute exposure to lethal doses of uranyl nitrate or uranyl acetate resulted in renal dysfunction in rats and mice as evidenced by increases in urine volume, plasma urea, blood urea nitrogen (BUN), and urinary total protein. Minimal histological alterations in the glomerulus, proximal tubules, and/or interstitium have been observed in rats and rabbits exposed to intermediate-duration doses of soluble uranium compounds as low as 0.05 mg U/kg/day; the severity of the renal lesions increased with dose. Additionally, a rabbit study demonstrated that renal lesions persisted up to 91 days following termination of a 91-day oral exposure. Chronic oral exposure to soluble uranium compounds resulted in minimal tubular damage at 81 mg U/kg/day and tubular atrophy at ≥140 mg U/kg/day. Due to the poor absorption of ingested insoluble uranium compounds, there are significant differences in the renal toxicity of various uranium compounds. No renal effects were observed in rats exposed to doses as high as 11,000–12,000 mg U/kg/day as uranium dioxide, uranium trioxide, uranyl octaoxide, or uranium tetrafluoride for 30 days; after 2 years of exposure to 11,000 mg U/kg/day as uranium tetrafluoride, mild tubular degeneration was observed in rats, but no adverse effects were observed in rats exposed to 12,000 mg U/kg/day as uranium dioxide for 2 years. In contrast, adverse renal effects were observed after a 30-day

exposure to doses of 140–270 mg U/kg/day as uranyl nitrate, uranium peroxide, or uranyl fluoride and doses of 440–790 mg U/kg/day as uranium tetrachloride or uranium acetate and a 2-year exposure to 81–170 mg U/kg/day as uranyl fluoride or uranyl nitrate. Available inhalation and oral exposure studies suggest that following exposure to low levels of uranium (doses or concentrations resulting in minimal renal effects), toxicity is not strongly influenced by the duration of exposure. As with other routes of exposure, proteinuria, renal failure, and renal lesions were observed in laboratory animals following acute dermal exposure to uranyl nitrate.

General damage to pulmonary structures, usually noncancerous alveolar epithelium damage of type II cells, can occur upon inhalation of insoluble reactive chemicals such as some uranium compounds (uranium tetrafluoride, uranium dioxide, uranium trioxide, triuranium octaoxide). In acute exposures, pulmonary damage may be limited to interstitial inflammation of the alveolar epithelium leading eventually to emphysema or pulmonary fibrosis. In studies of the pulmonary effects of airborne uranium dust in uranium miners, the respiratory diseases reported were aggravated by the insoluble aerosol particles (mine dust) to which these miners were exposed because most of the noncancerous respiratory diseases reported in these studies were consistent with toxicity of inhalable dust particles other than uranium, such as crystalline silica and diesel engine exhaust particles. Respiratory effects reported in workers acutely exposed to uranium hexafluoride were caused by hydrogen fluoride, a potent lung irritant and a spontaneous byproduct of the reaction between uranium hexafluoride and water, such as in mucous membranes. A follow-up study of three of the workers did not detect uranium in the lungs or evidence of lung damage 38 years after the initial exposure. Similar to human studies, signs of respiratory irritation (rhinitis and lung edema, hemorrhage, and emphysema) have been observed in animals exposed to ≥2 mg U/m^3 uranium hexafluoride, uranyl fluoride, and uranium tetrafluoride. It is likely that these effects were due to co-exposure to hydrogen fluoride. Inhalation exposure to insoluble uranium compounds also results in pulmonary damage. Very slight pulmonary lesions were observed in rats and dogs exposed to 16 mg U/m^3 as uranium trioxide for 4 weeks; mild to severe renal tubular necrosis was also observed at this concentration. In contrast, chronic exposure to 5.1 mg U/m^3 as uranium dioxide for at least 3.5 years resulted in lung fibrosis in monkey and dogs; renal effects were not observed in either species.

Limited data are available regarding reproductive effects of uranium in humans. Studies of uranium miners, millers, and processors found that male uranium miners had more first-born female children than expected, suggesting that uranium's alpha radiation damaged the y-chromosomes of the miners. However, the workers were also exposed to ^{222}Rn, chlorine, hydrofluoric acid, lead sulfate, nickel, nitric acid and nitrogen oxides, silicon dioxide, sulfuric acid, tobacco smoke, and diesel exhaust. Uranium

reduced fertility, likely due to reductions in spermatozoa counts, was observed in male mice exposed to ≥5.6 mg U/kg/day in drinking water and mated with untreated females. However, fertility was not significantly affected in another study in mice in which males and females were treated by gavage with up to 14 mg U/kg/day. These apparently discrepant results may be due to the different mode of dosing between the two studies (i.e., gavage vs. drinking water), which may have resulted in different rates of absorption. Uranium also reduced fertility in male rats dosed with 11.2 mg/kg/day and mated with untreated females; the NOAEL was 5.6 mg U/kg/day. Effects on female reproductive health have also been observed in mice orally exposed to uranium. Alterations in ovarian folliculogenesis were observed at ≥1.25 mg U/kg/day.

Developmental effects have been observed in the offspring of mice; these effects have often been observed at maternally toxic doses. Elevated uranium levels were measured in the offspring of rats exposed to uranyl acetate prior to mating and during gestation and lactation, suggesting transplacental and/or lactational transfer of uranium. The observed effects included lethality, reductions in growth, increase in visceral and skeletal abnormalities, and reproductive effects. Lethality effects consisted of reductions in viability on postnatal day 21 in offspring of mice dosed with 28 mg U/kg/day on gestation day 13 to postnatal day 21, decreases neonatal viability in the offspring of mice exposed to 5.6 mg U/kg/day prior to mating and throughout gestation and lactation, and increases in late resorptions and decreases in the number of live fetuses in the offspring of mice exposed to 14 mg U/kg/day prior to mating and during gestation. Reductions in fetal body weight were observed in the offspring of mice dosed with ≥2.8 mg U/kg/day on gestation days 6–15. This study also reported significant increases in the total number of external malformations at ≥2.8 mg U/kg/day and the total number of skeletal defects at ≥14 mg U/kg/day. Maternal toxicity may have played a role in this study since maternal weight gain during exposure was reduced by at least 33%. Alterations in ovarian folliculogenesis, similar to those described in the discussion of reproductive toxicity have been observed in the female pups of mice exposed to uranium prior to mating and/or during gestation; as discussed in the previous paragraph on reproduction toxicity, the doses tested in the study were much lower than effect levels reported in other studies, were below the detection limit, and are lower than normal background levels. In rats, doses of 22.5 or 45 mg U/kg/day administered from before mating until gestation day 14 were not fetotoxic; however, continued dosing during lactation resulted in a significant reduction in pup weight on postnatal day 21. Uranium did not affect developmental landmarks or neuromotor maturation in the pups, but the high dose altered learning and memory. Uranium was also shown to interfere with tooth eruption and development in young rats.

Since uranium is weakly radioactive, it has been assumed to be potentially carcinogenic at occupational levels by NIOSH. The International Agency for Research on Cancer (IARC) has no classification for uranium. Although significant increases in the occurrence of respiratory tract cancer (predominantly lung cancer) have been found in numerous studies of uranium miners, radon progeny in the mines, and not the uranium, were clearly identified as the carcinogenic agents. Exposure to crystalline silica and diesel engine exhaust, known human carcinogens, may also have contributed to carcinogenicity of the mine dust and their potential contributions have not been evaluated. Studies of workers at uranium milling or nuclear facilities and residents living near uranium mining and milling facilities have not found significant increases in cancer mortality associated with uranium exposure. There are limited data on the carcinogenicity of uranium in laboratory animals and no cancer bioassays with adequate numbers of animals and multiple concentration/dose levels were identified. Chronic-duration studies have not reported increases in the incidence of malignant tumors in hamsters exposed to 19 mg U/m^3 as carnotite uranium ore dust for 16 months; monkeys exposed to 5.1 mg U/m^3 as uranium dioxide for 5 years; dogs exposed to 8–8,815 mg U/kg/day as uranyl nitrate, uranyl fluoride, uranium tetrachloride, uranium tetrafluoride, or uranium dioxide for 1 year; or rats exposed to 664–12,341 mg U/kg/day as uranyl nitrate, uranium tetrafluoride, or uranium dioxide for 1 year. The limited number of animals tested and the less-than-lifetime exposure duration makes these studies less than ideal for evaluating the carcinogenicity of uranium. Several studies have found significant associations between uranium exposure and an increased incidence of malignant tumors. Increases in the incidence of pulmonary neoplasms were observed in dogs exposed to 5.1 mg U/m^3 as uranium dioxide for 5 years and rats exposed to 8.4 or 22 mg U/m^3 as uranium ore dust for 65 weeks. As with the negative carcinogenicity studies, these studies are also limited by the small number of animals tested and the less-than-lifetime exposure. The increases in the incidence of lung tumors may have been the result of uranium chemical toxicity, radiation exposure, or both.

Depleted Uranium. Like natural uranium, depleted uranium is primarily composed of ^{238}U, but has a smaller amount of ^{235}U and ^{234}U. Thus, depleted uranium is less radioactive than natural uranium. Although, the toxicity of depleted uranium has not been as well studied, the health effects associated with exposure to depleted uranium will be the same as natural uranium because the toxicity of natural uranium is primarily due to chemical toxicity to uranium rather than uranium radiotoxicity. Information on the toxicity of depleted uranium in humans comes from a series of studies of Gulf War veterans with embedded fragments containing depleted uranium. The studies examined a number of potential targets including the liver, kidney, bone, and the hematological, nervous, and reproductive systems. No significant alterations in biomarkers of liver function, bone turnover and metabolism, or hematological

function; neuroendocrine hormone levels; or sperm parameters were observed. Alterations in biomarkers of renal function (e.g., urinary retinol binding protein and β_2-microglobulin levels) were observed; however, the alterations were not statistically significant, as compared to veterans with normal urinary uranium levels. Although poorer performance on neurological tests were observed in Gulf War veterans exposed to depleted uranium from embedded fragments, the effects were not consistently observed, and were found to be strongly influenced by two subjects with extremely high uranium levels and severely complex co-morbid conditions.

A small number of animal studies have examined the toxicity of depleted uranium; these studies focused on renal toxicity and neurotoxicity. As with exposure to natural uranium, alterations in renal function and histopathology (swollen glomeruli, necrosis, and fibrosis) were observed in rats exposed to depleted uranium via fragments embedded in the gastrocnemius muscle. Acute exposure to depleted uranyl acetate in drinking water resulted in increased motor activity in male rats exposed to 28 mg U/kg/day and female mice exposed to 6 mg U/kg/day. No alterations were observed in tests of spontaneous motor activity in rats implanted with up to 20 depleted uranium pellets (approximately 760 mg depleted uranium) for 150 days. The difference in the exposure routes and the lack of data on blood and/or brain uranium levels from the drinking water studies and implantation study preclude a meaningful comparison of the three studies. No effects on spatial working memory were observed in rats dosed with 2.7 mg U/kg/day as depleted uranyl nitrate for 9 months. Investigators have tried to identify biochemical and morphological substrates that, when altered, could explain the behavioral alterations. Increased motor activity showed a weak correlation with increased lipid oxidation in the brain of rats in a 2-week study. Uranium also altered the levels of neurotransmitters and their metabolites in brain areas from mice and rats. Of various brain areas examined, the hippocampus from rats exposed to natural uranium in the drinking water for 90 days had the most uranium, suggesting that this area may play an important role in the neurobehavioral alterations caused by exposure to uranium. However, alterations in the levels of oxidative stress indicators were greater in other regions of the brain with lower uranium concentrations. Implantation of depleted uranium pellets in rats resulted in measurable uranium in the brain at 6–18 months after implantation and was accompanied by electrophysiological changes in hippocampal slices from the treated animals at 6 and 12 months, but not at 18 months. The mechanism(s) by which uranium induces neurological alterations is not known.

A decrease in the number of small primary ovarian follicles was found in mice exposed to ≥0.00039 mg U/kg/day in the drinking water for 30 days prior to breeding, during the mating period, and during gestation. However, all other follicle populations including primordial, secondary/growing, healthy, and

atretic were unchanged. It would be helpful to try to replicate these results because effects were reported at considerably lower doses than the adverse effect levels in other studies, effects were only observed in one type of follicle population, and the doses were below the detection limit and normal drinking water background levels. Uranium also showed estrogenic properties in mice at very low doses. Exposure of ovariectomized mice to depleted uranyl nitrate at 0.005 mg U/kg/day for 10 days or 0.009 mg U/kg/day for 30 days significantly increased uterine weight; an increase in the presence of cornified vaginal cells, indicative of an estrogenic effect, was also observed at 0.005 and 0.009 mg U/kg/day. However, these effects were not observed at higher doses (0.09 or 0.9 mg U/kg/day for 30 days). Again, it would be helpful to try to replicate these results observed at such low doses, particularly since the study only found effects at the lower doses tested, but not at the higher doses.

Exposure to depleted uranium did not alter the levels of serum testosterone or 17β-estradiol or the expression of transcription factors involved in the regulation of steroidogenic genes in male rats in a 9-month drinking water study.

Information on the carcinogenicity of depleted uranium is limited to an animal study that found an increased incidence of malignant fibrous histiocytoma at the depleted uranium implantation site in rats. However, an increase in tumors was only observed in the group with the largest implant.

Enriched Uranium. Enriched uranium is also primarily composed of ^{238}U, ^{235}U, and ^{234}U; however, the percentage of ^{235}U is increased to 2–4% (low enriched uranium) and >90% (high enriched uranium). The chemical toxicity of enriched uranium is the same as natural uranium; however, because enriched uranium is more radioactive than natural uranium, there is an increased risk of radiotoxicity. No human studies have examined the toxicity of enriched uranium and a limited number of animal studies on enriched uranium have been conducted. The chemical toxicity of uranium is identical to natural and/or depleted uranium; however, effects associated with exposure to radiation are also possible. Two studies have compared the toxicity of enriched uranium with that of depleted uranium. Enriched uranium, but not depleted uranium, increased serum testosterone and the expression of genes involved in steroidogenesis in male rats in a 9-month drinking water study. In addition, enriched uranium significantly increased the expression of transcription factors involved in the regulation of steroidogenic genes. These results suggested that the observed effects were mainly due to the radiation emitted by enriched uranium. Exposure to enriched uranium resulted in increases in the amount of paradoxical sleep and decreases in spatial working memory in rats dosed with 2.5–2.7 mg U/kg/day as enriched uranyl nitrate for 9 months. However, these effects were not observed in rats similarly exposed to depleted uranium. An additional

study reported delayed hyperactivity and decreased spatial memory in 5- or 9-month-old offspring of rats exposed to 4.3 mg U/kg/day as enriched uranyl nitrate in drinking water during gestation. A 9-month drinking water exposure to enriched uranyl nitrate resulted in increased serum testosterone levels in male rats. In addition, enriched uranium significantly increased the expression of transcription factors involved in the regulation of steroidogenic genes. These effects were not observed in rats similarly exposed to depleted uranium, suggesting that the observed effects were mainly due to the radiation emitted by enriched uranium.

2.3 MINIMAL RISK LEVELS (MRLs)

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

Although methods have been established to derive MRLs (Barnes and Dourson 1988; EPA 1990, 2012c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be reevaluated.

Minimal Risk Levels (MRLs) have been derived for the effects from inhalation and oral exposure to uranium, and those values are identified in this section and their bases are detailed in Appendix A. Although most of the health effects associated with exposure to natural uranium appear to be solely chemical in nature and not radiological and the contribution of the radiation toxicity to the overall mode of action is not known, the result of any combined chemical and radiological toxicity is accounted for in the study results. The chemical toxicity of depleted uranium is the same as natural uranium; however, the radiological toxicity of depleted uranium would be lower than natural uranium due to its lower specific

activity. Since the toxicity of natural uranium is primarily due to chemical toxicity, the MRLs calculated for natural uranium are applicable to depleted uranium. Exposure to enriched uranium is more likely to include a radiological component, but the data are limited. The toxicity of a variety of uranium compounds has been investigated in a number of animal species; the results of these studies support the findings of the available human studies. Regardless of the exposure duration or route, the animal data provide strong evidence that kidney damage is the principal toxic effect of uranium and that the toxicity varies according to solubility of the uranium compound. Other sensitive end points include the respiratory tract following chronic exposure to insoluble uranium compounds and developmental toxicity following acute oral exposure to soluble uranium compounds. The more soluble uranium compounds (uranium hexafluoride, uranium tetrachloride, uranyl fluoride, uranyl nitrate) have the highest renal toxicity, followed by the less soluble compounds (ammonium diuranate, sodium diuranate, uranium tetrafluoride) and the insoluble uranium compounds (uranium dioxide, uranium trioxide, uranium peroxide, triuranium octaoxide). The difference in toxicity is due to the easier absorption of soluble compounds from the lung or gastrointestinal tract into the blood and distribution to other tissues (Tannenbaum et al. 1951). The more insoluble uranium compounds have a greater potential for long-term respiratory toxicity due to long retention of the compound in the lung and may be due to chemical and/or radiological toxicity.

ATSDR has determined that the toxicity database for uranium justifies the derivation of separate MRLs for soluble and insoluble forms of uranium for certain durations and routes of exposure. This is based on toxicokinetic evidence that absorption of uranium (and concentration in target tissue) is significantly greater during exposure to the more water-soluble compounds. Where the database is not extensive enough to allow separate MRLs, the MRL for the soluble form should be protective for health effects due to all forms of uranium.

Inhalation MRLs.

Acute-Duration Inhalation MRL

There are limited data on the toxicity of uranium compounds in humans and animals following acute-duration inhalation exposure. Several case reports of individuals briefly exposed to uranium hexafluoride (Kathren and Moore 1986; USNRC 1986) or uranium tetrafluoride (Lu and Zhao 1990) are available. The observed effects included eye irritation and respiratory irritation, chemical burns, renal toxicity, and

gastrointestinal irritation; however, some of these effects may have been caused by the rapid release of hydrogen fluoride when uranium hexafluoride reacted with water in the air and mucous membranes.

Respiratory and renal effects have been observed in acutely exposed laboratory animals. Severe alveolar septal fibrosis was observed in rats exposed to 5,051 mg U/m^3 as enriched uranium dioxide for 100 minutes (Morris et al. 1990) and gasping and nasal irritation were observed in mice exposed to 637 mg U/m^3 as uranium hexafluoride for 10 minutes (Spiegl 1949). The renal effects included proteinuria and glucosuria in rats exposed to 426 mg U/m^3 for 10 minutes or 1,430 mg U/m^3 for 2 minutes as uranium hexafluoride (Leach et al. 1984) or in guinea pigs exposed to 23,040 mg U/m^3 as uranium hexafluoride for 2 minutes (Leach et al. 1984).

The available data were not considered adequate for derivation of an acute-duration inhalation MRL for uranium; the human studies did not reliably report exposure levels and the animal studies involved very short (<2 hours) exposure durations. Using one of the short exposure animal studies to derive an MRL may not be protective for continuous exposure for 2 weeks; longer-term animal studies with serial sacrifices (Stokinger et al. 1953) reported renal lesions following 3 days of exposure to soluble uranium compounds. These data are poorly reported and involved very small number of animals and are not suitable for MRL derivation.

Intermediate-Duration Inhalation MRL

- An MRL of 0.002 mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to insoluble compounds of uranium.

Intermediate-duration inhalation studies in animals have examined the toxicity of various insoluble uranium compounds including uranium dioxide, uranium peroxide, uranium trioxide, and triuranium octaoxide in several animal species. The results of these studies suggest that the kidney and the respiratory tract are sensitive targets of uranium toxicity, with the kidney being the most sensitive target. A summary of the adverse effect levels for renal effects identified in reliable intermediate duration studies is presented in Table 2-1. Renal effects were observed at ≥8.2 mg U/m^3; the severity of the lesions was concentration-related. Very slight tubular lesions were observed in dogs exposed to 8.2 mg U/m^3, and mild to severe necrosis was observed in rats, rabbits, and dogs exposed to 16 mg U/m^3. Although there are limited data to make species comparisons, data for uranium dioxide suggest that rabbits are more sensitive than rats, mice, or guinea pigs; the data do not allow for a comparison between rabbits and dogs. In addition to the renal effects observed in rats, rabbits, and dogs exposed to uranium trioxide, very slight

Table 2-1. Renal Effects Following Intermediate-Duration Inhalation Exposure to Insoluble Uranium Compounds

Species	Duration	NOAEL (mg U/m^3)	LOAEL (mg U/m^3)	Effect	Reference
Uranium dioxide					
Rat	5 weeks	19.4			Rothstein 1949b
Mouse	5 weeks	19.4			Rothstein 1949b
Rabbit	5 weeks		19.4	Marked tubular necrosis	Rothstein 1949b
Rabbit	7 months	10			Stokinger et al. 1953
Guinea pig	5 weeks	19.4			Rothstein 1949b
Guinea pig	7 months	10			Stokinger et al. 1953
Dog	5 weeks	1.1	8.2	Very slight tubular injury	Rothstein 1949b
Uranium peroxide					
Rabbit	23 days		15.4	Moderate necrosis	Dygert 1949d
Uranium trioxide					
Rat	4 weeks		16	Mild to severe necrosis	Rothstein 1949c
Rabbit	4 weeks		16	Mild to severe necrosis	Rothstein 1949c
Dog	4 weeks		16	Mild to severe necrosis	Rothstein 1949c
Triuranium octaoxide					
Rat	26 days	14			Dygert 1949c

pulmonary lesions were observed in dogs and rats exposed to 16 mg U/m^3 and severe effects were observed in rabbits dying early after exposure to 16 mg U/m^3 (Rothstein 1949c).

The lowest LOAEL for renal or pulmonary effects following intermediate-duration exposure to an insoluble uranium compound was 8.2 mg U/m^3 identified in dogs exposed to uranium dioxide for 5 weeks (Rothstein 1949b). In this study, groups of 6–19 dogs of unspecified strain and gender were exposed to 1.3, 9.3, or 10.4 mg/m^3 uranium dioxide (1.1, 8.2, or 9.2 mg U/m^3) 6 days/week for 5 weeks, presumably for 6 hours/day. The following parameters were used to assess toxicity: mortality, body weight changes, standard hematology, clinical chemistry, urinalysis, and histopathology. No dogs died from exposure to uranium dioxide dust. Additionally, no alterations in body weight gain or hematology, serum clinical chemistry, or urinalysis parameters were noted. Histopathological alterations were limited to the kidneys; "very slight" renal tubular degeneration was observed in two of six dogs at 8.2 mg U/m^3. No alterations were observed in two dogs examined from the 9.2 mg U/m^3 group. The results of this study are supported by the findings of slight to mild tubular degeneration in dogs exposed to 10 mg U/m^3 as uranium dioxide for 1 year; no effects were observed at 1 mg U/m^3 (Stokinger et al. 1953).

Benchmark dose (BMD) modeling was not used to estimate the point of departure due to the limited reporting of incidence data. The no-observed-adverse-effect level (NOAEL) of 1.1 mg U/m^3 was used to derive the MRL. This value was adjusted for intermittent exposure (6 hours/24 hours, 6 days/7 days) resulting in a $NOAEL_{ADJ}$ of 0.24 mg U/m^3. Because regional deposited dose ratios (RDDRs) are not available for dogs, dosimetric adjustments could not be made; thus, the $NOAEL_{ADJ}$ was used as the point of departure. The $NOAEL_{ADJ}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.002 mg U/m^3 for insoluble uranium compounds.

- An MRL of 0.0001 mg U/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to soluble compounds of uranium.

Intermediate-duration inhalation studies in animals have identified the kidney and lung as the most sensitive targets of toxicity following inhalation exposure to soluble or poorly soluble uranium compounds. The renal toxicity of various uranium compounds in several animal species is summarized in Table 2-2. These data demonstrate that the soluble uranium compounds are more toxic than the poorly soluble compounds, dogs, rabbits, and possibly rats are the most sensitive species tested, and guinea pigs are the least sensitive.

Table 2-2. Renal Effects Following Intermediate-Duration Inhalation Exposure to Soluble and Poorly Soluble Uranium Compounds

Species	Duration	NOAEL (mg U/m^3)	LOAEL (mg U/m^3)	Effect	Reference
Uranium hexafluoride					
Rat	30 days	0.05	0.2	Mild tubular damage	Spiegl 1949
Mouse	30 days	2	13.3	Severe degeneration, necrosis	Spiegl 1949
Rabbit	9 months		0.2	Very mild tubular injury	Stokinger et al. 1953
Guinea pig	30 days		13.3	Severe degeneration, necrosis	Spiegl 1949
Guinea pig	9 months	0.05			Stokinger et al. 1953
Dog	30 days	0.05	0.2	Mild tubular regeneration	Spiegl 1949
Uranyl fluoride					
Rat	5 weeks	0.5	2.2	Minimal degeneration	Rothstein 1949a
Guinea pig	5 weeks	2.2	9.2	Severe degeneration	Rothstein 1949a
Dog	5 weeks		0.15	Very slight degeneration	Rothstein 1949a
Uranyl nitrate					
Rat	30 days		0.13	Slight degeneration	Roberts 1949
Rabbit	6.5 months		0.25	Mild tubular atrophy	Stokinger et al. 1953
Guinea pig	6.5 months	2			Stokinger et al. 1953
Dog	30 days		0.13	Proteinuria	Roberts 1949
Uranium tetrachloride					
Rabbit	7.5 months	0.2			Stokinger et al. 1953
Guinea pig	7.5 months	0.2			Stokinger et al. 1953
Sodium diuranate					
Rat	5 weeks		15	Moderate degeneration, necrosis	Rothermel 1949
Rabbit	5 weeks		15	Degeneration, necrosis	Rothermel 1949
Ammonium diuranate					
Rat	30 days		6.8	Minimal necrosis	Dygert 1949b
Rabbit	30 days		6.8	Severe necrosis	Dygert 1949b
Uranium tetrafluoride					
Rat	30 days	4	18	Slight azotemia	Dygert 1949a
Rabbit	9 months	3			Stokinger et al. 1953
Guinea pig	30 days	4	18	Moderate-severe necrosis	Dygert 1949a
Guinea pig	9 months	3			Stokinger et al. 1953
Dog	30 days	0.5	3	Very slight degeneration	Dygert 1949a

In addition to the renal effects, pulmonary toxicity has been observed in animals particularly after exposure to uranium hexafluoride. Exposure to 2 mg U/m^3 for 30 days resulted in severe pulmonary edema in rabbits and slight pneumonia in dogs (Spiegl 1949). At higher concentrations (13.3 mg U/m^3), lung edema, hemorrhage, and emphysema were observed in rats, rabbits, and guinea pigs (Spiegl 1949). Since uranium hexafluoride is readily hydrolyzed to uranyl fluoride and hydrogen fluoride and hydrogen fluoride is a strong respiratory irritant resulting in pulmonary edema, it is likely that the observed respiratory effects are due to the hydrogen fluoride exposure. Respiratory effects have also been observed in rabbits and rats exposed to 6.8 mg U/m^3 as ammonium diuranate (Dygert 1949b). In rabbits, ammonium diuranate exposure (6.8 mg U/m^3) resulted in extensive respiratory tract irritation, evidence by nasal bleeding and pulmonary edema, hemorrhage, and necrosis. Respiratory irritation (nasal bleeding and interstitial bronchopneumonia) was also observed in rats exposed to 6.8 mg U/m^3. It is possible that these effects were secondary to the release of the ammonium ion, rather than uranium toxicity. Respiratory effects have not been consistently observed following exposure to other uranium compounds.

As presented in Table 2-2, dogs are the most sensitive species to the renal toxicity of uranium compounds. The lowest LOAEL values identified in dogs are 0.13 mg U/m^3 as uranyl nitrate for proteinuria (Roberts 1949) and 0.15 mg U/m^3 as uranyl fluoride for tubular damage (Rothstein 1949a). In the Roberts (1949) study, an increase in urinary protein excretion was observed between days 9 and 12 and then returned to normal; very mild histological changes, which the investigator noted were not of sufficient severity to be of concern, were observed in the renal cortex in two dogs exposed for 10 days. Since the two LOAEL values are almost identical, the Rothstein (1949a) study was selected as the basis of the MRL because it included histological examination of dogs exposed for an intermediate duration (the one dog examined at the end of the Roberts study had severe chronic nephritis, which precluded observing any possible uranium-induced renal effects). Although the lowest LOAEL value in rats (0.13 mg U/m^3) was similar to the lowest LOAEL values in dogs, the intermediate and chronic databases for soluble uranium compounds provide strong evidence that dogs are more sensitive than rats. In the Rothstein (1949a) study, groups of 2–6 dogs (strain and gender not specified) were exposed to 0.19, 2.8, or 12.2 mg/m^3 of uranyl fluoride dust (0.15, 2.2, or 9.2 mg U/m^3) for 6 hours/day, 6 days/week for 5 weeks. Clinical signs of toxicity, mortality, body weight changes, hematology, and blood and urine chemistries were monitored. At the termination of the study, the animals were sacrificed, selected organs were histopathologically examined, and uranium levels were determined. Anorexia, rhinitis, and polydipsia were observed in the two dogs exposed to 9.2 mg U/m^3; prior to death, vomiting blood, severe muscle weakness, and exhibited lassitude were observed. No deaths or clinical signs were observed at 0.15 or 2.2 mg U/m^3. Severe weight loss was also observed at 9.2 mg U/m^3; no alterations in body weight

gain were observed at 0.15 or 2.2 mg U/m^3. At 9.2 mg U/m^3, both dogs had increased blood nonprotein nitrogen (NPN) levels with the maximum value over 200 mg%. At 2.2 mg U/m^3, blood NPN and urinary amino acid levels were normal while one of three dogs had increased urinary protein levels. At 9.2 mg U/m^3, severe renal damage was seen in dogs. Moderate renal damage (no additional information provided) was observed at 2.2 mg U/m^3 and very slight damage was observed in about 50% of the dogs at 0.15 mg U/m^3.

A NOAEL/LOAEL approach was used to identify the point of departure for the MRL; BMD modeling was not used because incidence data were not available for all groups. The LOAEL of 0.15 mg U/m^3 for minimal renal lesions was used to derive the MRL. This value was adjusted for intermittent exposure (6 hours/24 hours, 6 days/7 days) resulting in a $LOAEL_{ADJ}$ of 0.032 mg U/m^3. Because RDDRs are not available for dogs, dosimetric adjustments could not be made; thus, the $LOAEL_{ADJ}$ was used as the point of departure. The $LOAEL_{ADJ}$ was divided by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.0001 mg U/m^3 for soluble uranium compounds.

Chronic-Duration Inhalation MRL

- An MRL of 0.0008 mg U/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to insoluble compounds of uranium.

There are limited data available to assess the toxicity of chronic exposure to insoluble uranium compounds. Slight to mild renal tubular degeneration was observed in dogs exposed to 10 mg U/m^3 as uranium dioxide for 1 year (Stokinger et al. 1953); no alterations were observed at 1 mg U/m^3. Although several tissues were examined histologically, significant alterations were only noted for the kidneys. Stokinger et al. (1953) also exposed rats to 1 or 10 mg U/m^3 as uranium dioxide, but no uranium-related alterations were observed. In a second chronic-duration study, no adverse effects were observed in rats or dogs exposed to 5.1 mg U/m^3 as uranium dioxide for 1–5 years (Leach et al. 1970). However, fibrosis in the tracheobronchial lymph nodes and fibrosis and metaplasia in the lungs were observed in dogs during a 6.5-year postexposure period (Leach et al. 1973). In monkeys, exposure to 5.1 mg U/m^3 resulted in lung fibrosis beginning after 3.6 years of exposure (Leach et al. 1970); the severity of the fibrosis increased with exposure duration. Fibrosis was also present in the lungs and tracheobronchial lymph nodes in monkeys sacrificed during the 6.5-year postexposure period (Leach et al. 1973). The investigators noted that the fibrosis may have been a radiotoxic effect based on the magnitude of the radiation dose, the absence of renal effects, and the similarity of the lesions to those observed following exposure to

plutonium dioxide; the alpha-radiation tissue doses were >500 rad (5 Gy) for the lungs and 7,000 rad (70 Gy) for the lymph nodes. However, it is unclear whether the damage was chemically or radiologically induced (or both); similar degenerative effects in the lungs have also been observed following prolonged exposure to diverse inorganic dusts. An elevation of blood NPN level was also observed in the monkeys during the postexposure period, but no histological alterations were observed in the kidneys (Leach et al. 1973).

Rhesus monkeys (5 males, 20 females) were exposed to 5.8 mg/m^3 uranium dioxide (5.1 mg U/m^3) 5.4 hours/day, 5 days/week for 5 years; the mass median particle diameter was 1.03 µm with a geometric standard deviation of 2.40. Another group of one male and five female monkeys served as controls. Groups of 1–2 monkeys were sacrificed after 1 day, 4 days, 15 days, 1 month, 2 months, 3 months, 5 months, 1 year, 1.5 years, 1.8 years, 1.9 years, 3.6 years, 4.1 years, or 4.7 years; two monkeys were sacrificed at 5 years. Six monkeys were observed for 6.5 years after exposure termination; two were sacrificed after 12 months, one after 6 years, and three after 6.5 years; the results of the recovery period examinations were reported in Leach et al. (1973). The following parameters were used to assess toxicity: general health, body weight, peripheral hematology, blood NPN levels, and histopathology of major tissues and organs. No uranium dioxide-related deaths were observed. No alterations in body weight, hematological parameters, or blood NPN levels were found. Histological alterations were limited to the lungs and tracheobronchial lymph nodes. After 2–3 months of exposure, granular black pigment accumulations were found in the lungs and tracheobronchial lymph nodes. After 3.6 years of exposure, slight fibrosis was observed in the lungs and hyaline fibrosis was observed in the tracheobronchial lymph nodes; the severity of the fibrosis increased with exposure duration and was not observed in the controls. Fibrosis was still present in the lungs and tracheobronchial lymph nodes 6.5 years postexposure.

The LOAEL of 5.1 mg U/m^3 was selected as the point of departure for the MRL; BMD modeling was not used due to the small number of animals sacrificed at each time period. The LOAEL was adjusted for intermittent exposure (5.4 hours/24 hours, 5 days/7 days) resulting in a $LOAEL_{ADJ}$ of 0.82 mg U/m^3. Because RDDRs are not available for monkeys, dosimetric adjustments could not be made; thus, the $LOAEL_{ADJ}$ was used as the point of departure. The $LOAEL_{ADJ}$ was divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.0008 mg U/m^3 for insoluble uranium compounds. A full uncertainty factor of 10 was used for extrapolation from monkeys to humans because no data were available to make dosimetric adjustments (pharmacokinetic component of uncertainty factor) and there are inadequate human data to assess potential differences in sensitivity between monkeys

and humans (pharmacodynamic component of uncertainty factor). A wide range of sensitivity has been found in animal species, but it is not known where humans would fall in the range of sensitivity.

- An MRL of 0.00004 mg U/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to soluble compounds of uranium.

There are limited human data on the chronic toxicity of soluble uranium. Thun et al. (1985) examined uranium mill workers exposed to yellowcake (26–86% ammonium diuranate), which was considered biologically soluble, for at least 1 year. Significant increases in urinary excretion of β_2-microglobulin and amino acids were observed in the uranium workers suggesting impaired renal tubular function. Clearance of β-2-microglobulin relative to that of creatinine was significantly associated with the length of time that the uranium workers had spent in the yellowcake area. Although urinary uranium levels were reported, atmospheric concentrations were not reported.

Stokinger et al. (1953) examined the chronic toxicity of uranium hexafluoride, uranium tetrachloride, and uranyl nitrate in dogs and rats following a 1-year exposure. Slight to mild renal tubular atrophy was observed in dogs and rats exposed to 0.2 mg U/m^3 as uranium hexafluoride or uranium tetrachloride; no effects were observed at 0.05 mg U/m^3. Exposure to uranyl nitrate resulted in mild to moderate tubular atrophy in dogs exposed to 0.25 mg U/m^3 (NOAEL of 0.15 mg U/m^3) and mild to marked tubular atrophy in rats exposed to 2 mg U/m^3 (NOAEL of 0.25 mg U/m^3).

The chronic-duration inhalation MRL for soluble uranium compounds was based on a 1-year dog study involving exposure to uranium tetrachloride (Stokinger et al. 1953). In this study, dogs of both sexes (11–12 males, 9–10 females) were exposed to uranium tetrachloride in inhalation chambers for 33 hours/week for 1 year at concentrations of 0.05, and 0.20 mg U/m^3. The animals were monitored for body weight alterations, clinical signs of toxicity, and biochemical alterations in the blood and urine. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined. All dogs survived the 1-year exposure period. No alterations in body weight gain, hematological parameters, or blood NPN levels were observed. Urinary protein levels were elevated, as compared to controls; however, pre-exposure levels were also elevated, precluding evaluating the clinical significance of the effect. Alterations in bromsulfalein retention test, indicating impaired liver function, were observed in the four dogs tested (0.2 mg U/m^3 group); no alterations in blood clotting times were observed. In the absence of histological evidence of liver damage, the change was not considered clinically significant. Renal tubular atrophy was observed in 2/16 dogs exposed to 0.05 mg U/m^3 (not

statistically significant using Fisher Exact test). Slight tubular atrophy in the inner cortex was observed in 7/14 dogs exposed to 0.2 mg U/m^3.

Data for the incidence of renal tubular atrophy were analyzed using all available dichotomous models in the EPA Benchmark Dose Software (BMDS, version 2.1.2) using the extra risk option; details of the BMD modeling are presented in Appendix A. The benchmark concentrations (BMCs) ranged from 0.032 to 0.082 mg U/m^3 and the 95% lower confidence limits on the BMCs (BMCLs) ranged from 0.019 to 0.054 mg U/m^3. A $BMCL_{10}$ of 0.019 mg U/m^3 was selected as a point of departure because it was estimated from the model providing the best fit to the incidence data. The $BMCL_{10}$ was adjusted for intermittent exposure (33 hours/168 hours) resulting in a $BMCL_{ADJ}$ of 0.0037 mg U/m^3. Because RDDRs are not available for dogs, dosimetric adjustments could not be made; thus, the $BMCL_{ADJ}$ was used as the point of departure. The $BMCL_{ADJ}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.00004 mg U/m^3 for soluble uranium compounds.

Oral MRLs.

Acute-Duration Oral MRL

- An MRL of 0.002 mg U/kg/day has been derived for acute-duration oral exposure (≤15 days) to soluble compounds of uranium.

There are limited human data on the oral toxicity of uranium. Signs of gastrointestinal irritation (nausea, vomiting, diarrhea) were observed in a subject ingesting 14.3 mg U/kg as uranyl nitrate in drinking water (Butterworth 1955); other potential targets of toxicity were not examined. Acute oral exposure studies in rats and mice have examined the lethality, systemic toxicity, neurotoxicity, and developmental toxicity of uranium. Information on the systemic toxicity is limited to two single-exposure toxicity study in rats (Domingo et al. 1987) and mice (Martinez et al. 2003) administered lethal doses and a repeated exposure study in mice (Ozmen and Yurekli 1998). In the 2 weeks following administration of a single gavage dose of 118 mg U/kg as uranyl acetate to rats, significant increases in urine volume (in the absence of changes in water consumption), plasma creatinine and urea, and urinary total protein and creatinine were observed; hyperemia and microhemorrhagic foci were also observed in the liver and kidneys at the end of the 2-week observation period (Domingo et al. 1987). In mice, administration of 166 mg U/kg as uranyl nitrate resulted in increases in blood urea and creatinine levels and proximal tubular necrosis (Martinez et al. 2003). Similarly, significant increases in BUN and creatinine levels were observed in mice exposed to

508 mg U/kg/day as uranyl acetate in the diet for 5 days (Ozmen and Yurekli 1998); the study did not include a histological examination of the kidney or other tissues. Neurological effects consisted of increased open field activity (line crossing and/or rearing) (Briner 2009; Briner and Murray 2005) in mice administered 28 or 6 mg U/kg/day as depleted uranyl acetate in drinking water for 2 weeks; exposure to 28 mg U/kg/day also resulted in a 53% decrease in body weight gain. Gestational exposure to ≥2.8 mg U/kg/day as uranyl acetate resulted in significant decreases in fetal body weights and increases in the occurrence hematomas in the fetuses of mice exposed on gestation days 6–15 (Domingo et al. 1989c); increases in the incidence of cleft palate were observed at ≥5.6 mg U/kg/day. Decreases in maternal body weight gain were observed at ≥2.8 mg U/kg/day. Exposure of neonatal rats (1 or 7 days of age) to 42.7 mg U/kg/day as uranyl nitrate administered via gavage in water, resulted in significant reductions in bone formation, increases in bone resorption, and diminished tooth development (Pujadas Bigi et al. 2003).

The available data provide evidence that the gastrointestinal tract, kidney, and developing organisms are target of uranium toxicity following acute oral exposure. Longer duration oral studies and inhalation studies identify the kidney as the most sensitive target of toxicity. The Domingo et al. (1989c) developmental toxicity study identified the lowest LOAEL (2.8 mg U/kg/day) and was selected as the basis of acute-duration oral MRL. In this study, groups of 20 pregnant Swiss mice were administered via gavage 0, 5, 10, 25, or 50 mg/kg/day uranyl acetate dihydrate (0, 2.8, 5.6, 14, or 28 mg U/kg/day) on gestation days 6–15. Body weights, food consumption, and general appearance were monitored daily. At termination, maternal liver and kidney weights were measured and uterine contents (number of implantation sites, resorptions, dead fetuses, and live fetuses) were evaluated. Live fetuses were evaluated for body weight, body length, sex, gross morphological abnormalities, visceral malformations, visceral anomalies, and skeletal defects. Significant decreases in maternal body weight were observed in all uranium groups; during the exposure period, the dams in the 2.6, 5.6, 14, and 28 mg U/kg/day groups weighed 33, 53, 75, and 88% less than controls, respectively. Significant decreases in food intake were also observed in the dams exposed to 5.6 mg U/kg/day and higher. A significant decrease in the number of live fetuses was observed at 5.6 mg U/kg/day, but was not observed at the two higher dose levels. No significant alterations in the number of early or late resorptions, number of dead fetuses, or sex ratio were observed. Significant decreases in fetal body weight were observed at ≥2.8 mg U/kg/day and decreases in fetal length were observed at ≥5.6 mg U/kg/day. Significant increases in the incidences of external defects were observed at 2.8 mg U/kg/day. The external alterations included cleft palate (significant at ≥5.6 mg U/kg/day) and hematomas (significant at 2.8 and 28 mg U/kg/day). The total number of skeletal defects was significantly increased at 14 and 28 mg U/kg/day; skeletal defects included bipartite

sternebrae (significant at 2.8, 14, and 28 mg U/kg/day), some metatarsal of hindlimb poorly ossified (significant at 14 and 28 mg U/kg/day), delayed ossification of skull (significant at 14 and 28 mg U/kg/day), and caudal reduced ossification (significant at 14 and 28 mg U/kg/day).

The results of the Domingo et al. (1989c) study suggest maternal body weight gain and fetal body weight and external and skeletal alterations as sensitive end points of uranium toxicity. It is possible that the developmental effects were secondary to the maternal toxicity; however, some of these effects may also be primary effects of uranium on the developing fetus. Thus, maternal and fetal end points were considered as the basis of possible points of departure for the acute-duration MRL. BMD modeling was used to identify potential points of departure for maternal and fetal effects. As described in greater detail in Appendix A, the number of litters with cleft palate, bipartite sternebrae, and total skeletal defects were analyzed using all available dichotomous models in the EPA BMDS (version 2.1.2) using the extra risk option and a benchmark response rate of 5%. The results of the BMD modeling are presented in Appendix A. The fetal body weight data and maternal body weight gain data were fit to all available continuous models in EPA's BMDS (version 2.1.2); however, none of the models provided an adequate fit to either data set.

The $BMDL_{05}$ values for cleft palate, bipartite sternebrae, and total skeletal defects were 0.20, 0.42, and 0.25 mg U/kg/day, respectively. The $BMDL_{05}$ of 0.20 mg U/kg/day for cleft palate was selected as the point of departure; this point of departure is lower than the $BMDL_{05}$ values for other fetal effects and is approximately 10-fold lower than the LOAEL for maternal and fetal body weight effects. Thus, it is likely to be protective of the other effects. The 0.2 mg U/kg/day point of departure was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an acute-duration oral MRL of 0.002 mg U/kg/day.

Intermediate-Duration Oral MRL

- An MRL of 0.0002 mg U/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to soluble compounds of uranium.

No studies have been identified that examined the toxicity of uranium in humans following an intermediate-duration oral exposure. A number of studies have examined the intermediate-duration oral toxicity of uranium in laboratory animals. Most of these studies involved exposure to soluble uranium compounds such as uranyl nitrate and uranyl acetate; there are limited data on poorly soluble or insoluble uranium compounds. The available data suggest that the kidney is the most sensitive target of uranium

toxicity; at higher dose levels, neurological, reproductive, and developmental effects have been reported. At lower concentrations, histological alterations have been observed in the proximal tubules, glomerulus, and/or renal interstitium in rats and mice exposed to uranyl nitrate in drinking water (Gilman et al. 1998a, 1998b, 1998c; McDonald-Taylor et al. 1992, 1997). At higher concentrations (40.38 mg U/kg/day), evidence of renal dysfunction (e.g., glycosuria, proteinuria) have also been observed (Gilman et al. 1998c). The Gilman et al. (1998a, 1998b) studies identified LOAELs of 0.06 and 0.05 mg U/kg/day for renal effects in rats and rabbits, respectively; neither study identified NOAEL values.

The LOAELs for neurological, reproductive, and developmental effects are similar and are about 50-fold higher than the LOAEL for renal effects. Neurological effects such as sleep and behavior alterations and decreased spatial memory were observed in rats exposed to 2.5–2.7 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2005, 2007b). However, no neurological effects were observed in rats similarly exposed to the same dose of depleted uranyl nitrate (Houpert et al. 2005). The investigators suggest that the observed effects may have been related to radiation toxicity. The reproductive effects consisted of decreases in male fertility in rats and mice following exposure to ≥5.6 mg U/kg/day as uranyl acetate (Linares et al. 2005; Llobet et al. 1991) and alterations in ovarian folliculogenesis in mice at ≥1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008; Feugier et al. 2008; Kundt et al. 2009). A recent study by Raymond-Whish et al. (2007) also reported alterations in ovarian folliculogenesis in mice, but the effects were at an extremely low dose (0.00039 mg U/kg/day). Additional data are needed to support whether reproductive effects occur at this dose level and to evaluate the toxicological significance of the observed effect (reduced number of small primary follicles, but no effect on primordial, secondary/growing, healthy, or atretic follicle populations). Developmental effects have been observed in rats and mice; most effects occurred at maternally toxic doses. The observed effects included neurobehavioral effects in the offspring of rats exposed premating and during gestation and lactation to 4.3 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2007a), decreases in pup body weight at ≥2.8 mg U/kg/day as uranyl acetate (Paternain et al. 1989; Sánchez et al. 2006), decreases in litter size, live fetuses, or viability at ≥14 mg U/kg/day as uranyl acetate (Domingo et al. 1989b; Paternain et al. 1989), and altered ovarian folliculogenesis in 3-month-old pups of dams exposed to 1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008).

The LOAELs of 0.05 and 0.06 mg U/kg/day for kidney effects in rats and rabbits (Gilman et al. 1998a, 1998b) were considered as possible points of departure for an intermediate-duration oral MRL for soluble uranium compounds. Although the rabbit study identified the slightly lower LOAEL, the rat LOAEL was selected as the point of departure for the MRL due to possible subclinical infection in the rabbits. Gilman

et al. (1998b, 1998c) conducted two 91-day studies in rabbits. The kidney uranium levels for the two studies were not comparable; rabbits in the first study (Gilman et al. 1998b) had higher kidney uranium levels than in the second study (Gilman et al. 1998c) even though the dose was lower in the first study (28.70 mg U/kg/day dose and 4.98 µg U/g kidney level in the Gilman et al. 1998b study compared to 40.98 mg U/kg/day dose and 3.48 µg U/g kidney level in the Gilman et al. 1998c study). In the Gilman et al. (1998b) study, the male rabbits were not SPF derived and four animals developed *Pasteurella multocida* infections during the study; Gilman et al. (1998c) suggested that even though the affected rabbits were removed from the study, it is possible that other animals had a subclinical infection and that this may have increased sensitivity. Thus, the rat study was selected as the basis of the MRL; the rats used in the Gilman et al. (1998a) study were SPF derived. The Raymond-Whish et al. (2007) study was not selected as the point of departure because there are no other data to support this extremely low value and the toxicological significance of this slight change in one follicle population is not known.

In the Gilman et al. (1998a) study, five groups of Sprague-Dawley rats (15/sex/dose, 60 g) were exposed to uranium as uranyl nitrate in drinking water (0, 0.96, 4.8, 24, 120, and 600 mg/L) for 91 days. Time-weighted average doses (as mg U/kg/day) calculated by the authors from fluid intake data were <0.0001 (control group), 0.06, 0.31, 1.52, 7.54, and 36.73 mg U/kg/day in males and <0.0001 (controls), 0.09, 0.42, 2.01, 9.98, and 53.56 mg U/kg/day in females. Clinical signs were monitored daily and body weights were measured weekly; fluid intake and feed consumption were also measured, but the frequency was not reported. Hematological and serum clinical chemistry parameters, organ weights, and histopathology examination of major tissues and organs were assessed at termination. Hematological and biochemical parameters were not affected in a significant exposure-related manner. Statistically significant increases in renal lesions included cytoplasmic vacuolization, tubular dilation, and lymphoid cuffing in males at ≥0.06 mg U/kg/day; capsular sclerosis, tubular anisokaryosis, and interstitial reticulin sclerosis in females at ≥0.09 mg U/kg/day; nuclear vesiculation in males and females at ≥0.06/0.09 mg U/kg/day; and glomerular adhesions and cytoplasmic degeneration in males at ≥0.31 mg U/kg/day. Lesions were also observed in the liver at all doses including anisokaryosis, vesiculation, increased portal density, perivenous vacuolation, and homogeneity; the investigators considered these adaptive and likely reversible. Thyroid lesions were observed in both sexes (multifocal reduction of follicular size, increased epithelial height in males at 0.31 mg/kg/day and females at 2.01 mg/kg/day). A decreased amount and density of colloid in the thyroid was observed in males only. Sinus hyperplasia of the spleen was observed in males and females at 36.73/53.56 mg/kg/day.

An attempt was made to fit the incidence data to BMD models; however, none of the models provided an adequate fit. Thus, a NOAEL/LOAEL approach was used to derive the MRL. The LOAEL value of 0.06 mg U/kg/day for renal effects in rats (Gilman et al. 1998a) was divided by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animals to human extrapolation, and 10 for human variability) resulting in an intermediate-duration oral MRL of 0.0002 mg U/kg/day for soluble uranium compounds. A partial uncertainty factor was used to extrapolate from a LOAEL because the histological alterations observed at 0.06 mg U/kg/day were considered minimally adverse.

There are inadequate data to derive an MRL for insoluble uranium compounds (e.g., uranium tetrafluoride, uranium trioxide, uranium dioxide, uranium peroxide, triuranium octaoxide). The toxicity of insoluble uranium compounds were tested in a series of 30-day studies conducted by Maynard and Hodge (1949). No histological alterations were observed at the highest uranium dioxide, uranium trioxide, uranyl octaoxide, or uranium tetrafluoride doses (11,000–12,000 mg U/kg/day). By comparison, renal lesions were observed following exposure to 200 mg U/kg/day as uranyl nitrate. These data suggest that the toxicity of soluble uranium compounds are at least an order of magnitude higher than for insoluble uranium compounds.

Chronic-Duration Oral MRL

Available data on the chronic oral toxicity of uranium comes from several ecological studies examining the possible association between elevated levels of uranium in drinking water and alterations in kidney function (Kurttio et al. 2002, 2006a; Limson Zamora et al. 1998, 2009; Mao et al. 1995; Seldén et al. 2009). Associations between parameters of renal dysfunction (e.g., urine levels of albumin, β_2-micro-globulin, glucose, and protein HC) and elevated uranium levels in drinking water were observed in some of the studies (Kurttio et al. 2002; Limson Zamora et al. 1998, 2009; Mao et al. 1995; Seldén et al. 2009). These studies did not find overt signs of toxicity and in many cases, the biomarkers of renal dysfunction were within the normal range. Although most of the epidemiology studies provided information on uranium levels in the drinking water, there was often a large range of exposure levels; thus, the human oral exposure studies do not provide reliable dose-response data.

Chronic-duration oral studies have been conducted in rats exposed to uranyl fluoride, uranyl nitrate, uranium dioxide, or uranium tetrafluoride in the diet for 2 years (Maynard and Hodge 1949; Maynard et al. 1953) and in dogs exposed to uranyl fluoride, uranyl nitrate, uranium tetrachloride, uranium tetrafluoride, or uranium dioxide in the diet for 1 year (Maynard and Hodge 1949; Maynard et al. 1953).

As with shorter durations of exposure, these studies identify the kidney as the most sensitive target of uranium toxicity. In rats, minimal tubular damage primarily consisting of regeneration of tubular epithelium was observed at the lower doses of soluble uranium compounds, 81 mg U/kg/day as uranyl fluoride and 170 mg U/kg/day as uranyl nitrate. At higher doses (140 mg U/kg/day as uranyl fluoride and 330 mg U/kg/day as uranyl nitrate), tubular atrophy was observed; the severity of the atrophy and extent of the damage increased with dose. For the less soluble uranium tetrafluoride, minimal tubular degeneration was observed at the highest dose tested, 11,000 mg U/kg/day; no adverse effects were observed in rats exposed to 12,000 mg U/kg/day as uranium dioxide (Maynard and Hodge 1949; Maynard et al. 1953). In dogs, renal tubular atrophy was observed following a 1-year exposure to 7.7 mg U/kg/day as uranyl fluoride, 9.5 mg U/kg/day as uranyl nitrate, 31 mg U/kg/day as uranium tetrachloride, 150 mg U/kg/day as uranium tetrafluoride, or 900 mg U/kg/day as uranium dioxide; the uranyl fluoride study also found slight renal damage in dogs exposed to 1.9 mg U/kg/day for 1 year. As with the rat studies, the dog studies showed that the severity and extent of the renal damage increased with dose. The highest NOAELs in the dog study were 0.77 mg U/kg/day as uranyl fluoride and 6.2 mg U/kg/day as uranium tetrachloride; NOAELs were not identified in the uranyl nitrate, uranium tetrafluoride, or uranium dioxide studies.

The dog study of uranyl fluoride identified the lowest LOAEL (1.9 mg U/kg/day); however, the dog studies are not a suitable basis for an MRL because only two dogs of unknown strain and gender were tested at each dose level. The rat studies of uranyl fluoride and uranyl nitrate appear to be the most suitable basis for a chronic-duration oral MRL. A NOAEL of 0.54 mg U/kg/day and a LOAEL of 81 mg U/kg/day were identified for uranyl fluoride and a NOAEL of 33 mg U/kg/day and a LOAEL of 170 mg U/kg/day were identified for uranyl nitrate (Maynard and Hodge 1949; Maynard et al. 1953). In the uranyl fluoride study, which identified the lowest LOAEL, groups of 15–25 male and 15–25 female rats (strain not specified) were exposed to diets containing 0, 0.01, 0.05, 0.1, 0.15, 0.25, 0.5, or 0.75% uranyl fluoride (0, 5.4, 27, 54, 81, 140, 270, or 400 mg U/kg/day) for 2 years. The animals were monitored for body weight alterations, clinical signs of toxicity, hematology, and biochemical alterations in the blood and urine. At the termination of the study, the surviving animals were sacrificed and selected organs were histopathologically examined. All rats in the 400 mg U/kg/day group died within the first 2 months of the study. At 270 mg U/kg/day, increased mortality was observed, with only 50% of the animals surviving the first year of exposure. At the end of the first year, decreases in body weight gain of >10% were observed at 270 mg U/kg/day in males (30%) and females (18%); at the end of 2 years, >10% decreases in body weight gain were observed at 140 mg U/kg/day in males (11%) and females (15%) and at 270 mg U/kg/day in males (20%) and females (28%). Decreases in red blood cell counts and hemoglobin levels

and increases in white blood cell counts were observed in males at 140 and 270 mg U/kg/day. Histopathological alterations were observed in the kidneys at doses of ≥81 mg U/kg/day. Marked renal tubular atrophy was observed at 140 and 270 mg U/kg/day, with a dose-related increase in severity of the lesions. At 81 mg U/kg/day, 2/5 rats examined showed traces of renal tubular alterations. No other uranium-related effects were noted.

Derivation of an MRL using the NOAEL of 54 mg U/kg/day identified in the 2-year uranyl fluoride rat study (Maynard and Hodge 1949; Maynard et al. 1953) as the point of departure was considered; the NOAEL/LOAEL approach was used because the lack of incidence data for most exposure groups precluded using benchmark dose analysis to identify a point of departure. Using this point of departure would result in an MRL that is higher than the intermediate-duration oral MRL for uranium; thus, a chronic-duration oral MRL has not been derived.

The results of a serial study in which rats were exposed to several doses of uranyl nitrate in the diet for up to 1 year (Maynard et al. 1953) coupled with the rat 2-year study (Maynard and Hodge 1949; Maynard et al. 1953) suggest that at low exposures, the renal tubular epithelium is regenerated and continued exposure does not result in more severe effects. However, at higher doses, the capacity to regenerate the renal tubular epithelium is exceeded and tubular atrophy is observed. In the serial study (Maynard et al. 1953), exposure to 170 mg U/kg/day as uranyl nitrate in the diet resulted in regeneration of the renal tubular epithelium after 2 weeks of exposure; there was no progression of renal damage with continued exposure and the renal tubules in rats exposed for 2 weeks were similar to those exposed for 1 year. Additionally, a 2-year exposure to 170 mg U/kg/day did not result in any further damage to the kidneys (Maynard and Hodge 1949; Maynard et al. 1953). In contrast, regeneration was observed in the first month of the exposure to 660 mg U/kg/day; however, with continued exposure, tubular atrophy was observed at 6–8 weeks. The severity of the atrophy and the areas of the kidney affected by uranium increased with duration. Given these data on the ability of the kidney to repair renal damage at low doses, the intermediate-duration oral MRL may be protective for chronic exposures.

2. RELEVANCE TO PUBLIC HEALTH

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